Vol. XLVII. No. 177. AUTUMN, 1930.

# The Bristol Medico-Chirurgical Journal

PUBLISHED UNDER THE AUSPICES OF

THE BRISTOL MEDICO-CHIRURGICAL SOCIETY.

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## CONTENTS.

| | Page |
|---|---|
| Observations on Epilepsy. By J. W. Bligrodon, C.B.E., M.D. | 169 |
| Five Years' Experience of Surgery in Exophthalmic Goitre. By A. Rendle Short, B.Sc., M.D., B.S., F.R.C.S. | 185 |
| The Treatment of Graves' Disease. By C. D. K. Herapath, M.D., M.D. | 193 |
| Changes in the Spleen in Acute Pyogenic Infections. By T. E. W. Hewer, M.D. | 197 |
| A Case of von Recklinghausen's Disease (Multiple Neuro-fibromata) with Spontaneous Fractures. By L. R. Ashton | 210 |
| The Origin and Significance of Tuberculosis of the Tracheo-Bronchial Lymph Nodes of the Lung. By L. R. Jordan | 225 |
| Reviews of Books | 239 |
| Editorial Notes | 248 |
| The Medical Library of the University of Bristol | 252 |
| Local Medical Notes | 254 |

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# The Bristol Medico-Chirurgical Journal

*"Scire est nescire, nisi id me*
*Scire alius sciret."*

AUTUMN, 1930.


## OBSERVATIONS ON EPILEPSY.*


BY

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The term epilepsy, from ἐπίληψις a seizure, or taking hold of, formerly had a very definite meaning, and was applied only to those cases in which there was a sudden attack of unconsciousness accompanied by convulsions. Of late years, however, it has been used in connection with so many attacks, including migraine, narcolepsy, pyknolepsy, vaso-vagal and even occasional slight syncopal attacks, that the best definition would appear to be a temporary paroxysmal disorder, not hysterical, of any part of the nervous system. Thus there may be as many epilepsies as there are parts of that system, the symptoms depending upon the part implicated, and as it has been suggested

* Read at a meeting of the Bristol Medico-Chirurgical Society, on 14th May, 1930.

that even the sympathetic ganglia may be subject to epilepsy, the definition cannot be confined to the central nervous system. The object of this paper, however, is to discuss that form, the old "falling sickness" or so-called idiopathic epilepsy, which is characterized by loss of consciousness and convulsive seizures, and frequently associated with various forms of mental derangement.

The three points that I propose to consider are: (1) The possible or probable cause of the attack; (2) the seat of origin of the impulses which originate the convulsion; (3) the relation of the seizures to the mental disturbances occurring immediately before, after and between the attacks.

James Collier, in his Lumleian Lectures in 1928, discusses the probable cause of this disease, and suggests that the irritant causing the attack is probably a toxin formed in some metabolic dyscrasia, that this particular toxin may not be confined to those suffering from epilepsy, but that in them some part of the central nervous system is congenitally weak and susceptible to the stimulant effects of the poison. In support of this theory he quotes the results of experiments on animals, by which it was shown that when certain poisons were administered a smaller dose was required to produce convulsions in those in which the central nervous system had been damaged than in animals in which it was intact. He says also that an endocrine origin has been suggested, but thinks the theory he has advanced the more probable.

W. G. Lennox and Stanley Cobb have dealt very exhaustively with the question of the origin of the seizures, and after analysing the statistics of various writers and the results of experiments, conclude that at present nothing is known as to the exciting cause.

In certain cases of epileptiform seizures they think that acidosis acts as a sedative to nerve cells, alkalosis renders them more excitable. They find that abstinence from meat has no beneficial effect, but in some cases fasting lessens the number of seizures. They appear to suggest that an ordinary amount of meat with plenty of fat and cream is more likely to be beneficial than a carbohydrate diet.

I have come across one case, a male epileptic, whose fits are always worse after taking eggs. On one occasion, while taking luminal, he had been going on very well for some time, but about four hours after having an egg he had a strong fit, and he told me that he had not had an egg before for more than twelve months, as they always made him worse.

Though numerous experiments have been tried and observations made, the subject seems far from being settled, but their periodicity, the fact that as a rule they commence at that period of life when certain endocrine glands are becoming mature, that once started they tend to continue throughout life, and that the effects of dieting are so disappointing, all point to an endocrine origin, the trouble being due, perhaps, to the excessive secretion of a hormone; or (what is more probable) the secretion is normal, but the part of the nervous system implicated is, as Collier suggests, congenitally weak and susceptible.

The next question is, which part of the central nervous system is responsible for starting the convulsions? Hughlings Jackson, in his Lumleian Lectures in 1890, said he was of opinion that the primary discharge was from the cells of the highest level, probably those in front of the Rolandic area, which he looked upon as the highest motor cells, in other words the cells which originate the most complex groups of

movements. Other neurologists have suggested various sites, from the cord to the cortex; but the majority still hold that the discharge occurs in some part of the cortex, the clonic character of some of the convulsions being adduced as evidence. That the cortex is involved can scarcely be in doubt, but there appears to be a good deal of evidence in favour of its implication being secondary to impulses arising in some other part of the nervous system, probably the corpus striatum.

In the first place, those seizures which are known to originate in the cortex, constituting cortical or Jacksonian epilepsy, differ materially from the major attacks, which are characteristic of so-called idiopathic epilepsy. The twitching of the muscles spreads deliberately, seldom involving those of the whole body, consciousness is rarely lost completely, and when it is lost this occurs late in the attack, whereas in the idiopathic form consciousness is lost before the convulsions commence, and these become general so quickly that it is almost impossible to follow the sequence of events.

In an affection in which symptoms of mental alienation, due to cortical derangement, are so common, were the cortex the primary seat of the trouble we should expect those symptoms to occur even more frequently than they do, and to arise earlier in the course of the case.

In general paralysis seizures indistinguishable from those of epilepsy frequently occur. At one time it was thought that the characteristic cry was the distinguishing feature of epilepsy; yet I have heard it at the commencement of an epileptiform convulsion in a general paralytic, and it is often absent from a true epileptic attack. Now, although this disease affects

every part of the nervous system, in the majority of cases, if not in all, it commences in the cortex, and is fairly advanced there before showing evidence of the involvement of deeper structures. If the seizures are cortical in origin they should occur early, but as a rule they do not, and when they do the prognosis as regards life is grave, the case running a rapidly fatal course, showing that the centres more deeply seated were attacked early.

The epileptiform attacks in cases of alcoholism do not occur early, as we should expect did they arise primarily in the cortex, alcohol affecting that region first. As a rule, they come on quite late in the case, and though some patients addicted to alcohol become confirmed epileptics, this only occurs after a long period of intemperance.

A certain proportion of cases of epilepsy commence late in life, when there is every reason to think it may be due to arterial degeneration. In these again the seat of the mischief does not appear to be the cortical cells, for many senile dements show marked changes in this region who have never had a seizure. I can call to mind one in whom almost the whole frontal cortex had atrophied and the patient talked incoherent nonsense, but had never had a convulsion. The evidence in these cases seems to point to general epileptiform convulsions having their seat of origin in some other part than the cerebral cortex.

Some years ago I searched the post-mortem records of the Bristol Asylum for the previous twenty years to discover all cases in which a lesion strictly limited to the basal ganglia had been found, and compared the results with the notes taken during life. There were seventeen in all, and were as follows :—

| *Site of Lesion.* | | *Clinical Picture.* | |
|---|---|---|---|
| Optic thalamus .. | 3 | Dementia, no paralysis, no convulsions .. .. | 3 |
| Optic thalamus and corpus striatum.. | 3 | Dementia .. .. .. | 1 |
| | | Seizures, paralysis, dementia, speech much affected .. .. .. | 1 |
| | | Seizure with strong convulsions.. .. .. | 1 |
| Corpus striatum .. | 10 | Speech affected .. .. | 4 |
| | | Hallucinations of sight and hearing .. .. | 1 |
| | | Epilepsy, dementia, destructiveness .. .. | 1 |
| | | Fits two or three years before admission .. | 1 |
| | | Left-sided convulsions.. | 1 |
| | | Epileptiform fits .. .. | 1 |
| | | Pupils normal, knee-jerks present .. .. .. | 1 |

In one of the cases in which speech alone was affected the patient, a woman nearly seventy years of age, had several transient attacks of aphasia, in which she was slightly giddy, and could not remember words in the middle of conversation. Post-mortem, the only lesions found were several small spots of softening in the corpus striatum. From this table it seems that lesions of the thalamus alone do not give rise to any motor trouble, but that lesions of the corpus striatum are frequently accompanied by convulsions or aphasic attacks, or both.

Acute distension of the lateral ventricles with fluid will also cause general convulsions. The following case may be of interest in this connection.

A female, aged 43, was admitted to the Bristol Asylum on 13th October, 1919. She was single, and suffering from mania and epilepsy. The following history was obtained from her brother and sister :—

When two years old she had convulsions, but soon recovered and was apparently normal till she was seventeen, when she had a bad breakdown, apparently an attack of manic-depressive insanity, and was in bed for eight weeks or more at home. Her chief delusion was that they were going to bury her alive. She recovered from this, but had a similar attack when she was twenty-two, and another when twenty-six ; between them she was facile and childish, but of a very nice disposition, always willing to help anyone. Sometime in the year 1916, when about forty, she became strange, at times complaining of pain in her head, and on several occasions when sitting or talking to her brother or sister it was noticed that she became pale, extended her legs, and turned her head and eyes up and to one side. She did not appear to lose consciousness completely, however, though for a few seconds after the turns she was lost and confused. She became so dirty in her habits, quarrelsome and disagreeable to those around her, that her relatives were compelled to have her placed under restraint. On admission she was very irresponsible and with little memory for recent events, thought her friends were trying to defraud her, and was disagreeable and rude if addressed.

On 19th October she had a series of epileptiform seizures and was unconscious. By the 21st she had had about two hundred attacks, but had regained consciousness and complained of pain in her head. On 25th October she was much better, but had pain in the calf of the left leg and the left tendo achillis seemed unduly rigid. On 9th November she complained at times of pain in the head and noises in the right ear. On 10th June, 1920, she is noted as giving no trouble ; on 21st October, 1921, as maintaining her physical condition, and very cheerful ; on 25th March, 1922, as being childish and good-natured and doing some sewing in the ward. After this she went on very well, did useful sewing, was happy and agreeable to those around her, and was about to be sent to her friends on trial, when she developed an attack of pneumonia from which she died on 22nd December, 1922.

At the post-mortem examination the pia-arachnoid was found thickened but stripped easily. The posterior part of the callosal convolution on the right side, as also the right hippocampal gyrus, was yellow and soft, and the posterior part of

the corpus callosum was wasted and yellow. The ventricular ependyma was granular, and in the right choroid plexus was a fair-sized, shrivelled mass which, by its pressure, had caused considerable atrophy of the right corpus striatum. After it had been in formalin some time Dr. Hadfield dissected the specimen, and said that it was an old hydatid cyst which had apparently dried and shrivelled up.

I have given the history of the case at some length because it is quite open to anyone to believe that this was one of ordinary idiopathic epilepsy, with the choroid hydatid as a coincidence. From the nature of the early attacks, the temperament of the patient between them, the absence of any symptoms of a fit or of *petit mal* from the age of two till she was forty, and the fact that though she had such a series of attacks shortly after her admission she had had none for many months before her death and had been so much more agreeable and amenable, I am led to believe that the hydatid cyst was the cause of the seizures through its pressure on the corpus striatum. If that be so, it supports a belief that not only may seizures indistinguishable from true epileptic attacks be caused by irritation of the striate body, but that the irritation which causes the fits may also give rise to that peculiarly irritable temperament which we so often meet in epileptics.

Whatever view may be taken of this particular case, there appears, at any rate, a fair amount of indirect evidence in favour of the view that the impulses which start the epileptic seizure originate in a subcortical centre, most probably the corpus striatum. This would account for the very rapid spread of the convulsion to all the muscles of the body, and for the similarity of the seizures of general paralysis and of pressure on the corpus striatum to those of the ordinary epileptic fit; whereas, if it is held that the epileptic convulsion is cortical in origin, it is difficult

to account for the difference between the Jacksonian seizure which is known to be cortical and the attack in idiopathic epilepsy.

One other fact appears to have considerable bearing on this subject. All who have had much to do with epileptics must have noticed in many cases that the character of the voice is peculiarly modified, being uninflected and wooden in type. Scripture has described this condition of voice in the epileptic, and maintains that by taking a record of the speech vibrations he is able to diagnose any case of epilepsy, as the character is quite impossible of imitation by the non-epileptic. Kinnier Wilson, in discussing progressive lenticular degeneration and comparing its symptoms with those of paralysis agitans, mentions that in early cases of the former disease, as also in the latter, the character of the voice is altered. He says: "The patient's utterance is monotonous and sometimes dysarthric. To use a picturesque French expression: 'Il a perdu le chanson du lange.'"

It can hardly be a coincidence that an alteration in the tone of voice should occur in these two diseases, which are known to be due to affection of the corpus striatum, and also in epilepsy.

In what way is the corpus striatum concerned in connection with the motor system? The optic thalamus, besides being the relay ganglion in the course of the afferent sensory nerves, is also a centre for the association of the special senses, notably of sight and touch, whereby our elementary perceptions of objects are formed. Our perception of the size, position and form of those objects is dependent upon our sixth or muscular sense. Just as the senses of sight and touch have to be associated with each other, so has the muscle sense to be associated with

them. As Herbert Spencer says: "There cannot be co-ordination of many stimuli without some ganglion through which they are brought into relation." And in the case of our sixth or muscle sense, with its enormous number of incoming stimuli associating it with all the other senses, that ganglion is the neo-striate part of the corpus striatum.

We have seen that it is intimately connected with the motor system, and that in lesions of parts of it there is frequently loss of muscle sense association evidenced by various forms of aphasia. We think in terms of muscle sense; in other words, every idea is an incipient muscular contraction. Hughlings Jackson in his Lumleian Lectures said: "When a healthy person thinks of doing something (has an idea of movement), I consider that what occurs physically is slight discharge not only of sensory but also of motor arrangements of his highest centres, there is nascent movement, slight discharge of the very same motor nervous arrangements of the highest centres which, if more strongly discharged, would, by intermediation of middle and lowest centres, produce the actual movement."

In paralysis agitans a common and distressing symptom is the inability to commence certain movements, it may be to get up out of a chair or start walking.

In aphasics it is common for the patient to forget words in the middle of a sentence, or to be unable to name objects at sight. Hughlings Jackson in his Croonian Lectures mentions the fact that aphasics can sometimes use and protrude the tongue which is not paralysed, but cannot put it out if asked to do so, though they evidently understand what is said to them, and will sometimes put the hand to the mouth to try and pull the tongue forward. In these cases there

is no paralysis of motion, for the muscles can be used freely, and the required action is sometimes performed by the patient when not asked to do so. The inability is not due to an aboulia, for that is an affection of will power. It is not negativism, for the patients are perfectly willing and wish to perform the act required. In all these cases it would appear to be due to the inability to form the idea.

When a person wishes to rise from his seat or to perform any act those sensori-motor cells which will be concerned must first be mildly stimulated, giving rise to the idea. Upon further stimulation the idea becomes the act. In the absence of fibres and cells carrying impulses to those groups of cells in the sensori-motor region the idea cannot be aroused, or in other words a mental picture cannot be produced. These association impulses arise from various parts and in various ways. In the case of paralysis agitans they are aroused by the sight of another person whom he wishes to greet, or by the sound of someone requesting him to rise, and the same applies to the patient who cannot name articles at sight or protrude his tongue at will. In all these cases the failure is due to the inability of the association-currents to reach and excite those groups of sensori-motor cells which will be concerned in the movement, and if the corpus striatum be the centre for the association of muscle sense with all the others, lesions in its several parts will account for the various forms of aphasia, as word blindness, word deafness, etc.

It has been held for some time by many authorities that the corpus striatum is not connected with the cerebral cortex by direct fibres. Kinnier Wilson and Victor Horsley in 1914 carried out a number of carefully-planned and interesting experiments on the corpus striatum in apes, every precaution being taken to

prevent injury to surrounding structures, and the results at which they arrived may be summed up as follows: (1) No direct fibres could be traced to the cortex or to the spinal cord; (2) there are no apparent fibres between the corpora striata of the two sides; (3) fibres from the caudate nucleus and putamen pass direct to the globus pallidus; (4) fibres from the globus pallidus pass in the thalamic fasciculus through the lower part of the internal capsule to end in the thalamus; (5) another strand, the strio-subthalamic or ansa lenticularis, leaves the globus pallidus and divides into two parts. One passes to the corpus subthalamicum, the other to the red nucleus. From this it seems that though impulses from the striate body do not pass by a direct route to the cortex they can, and no doubt do, by the more indirect path, namely, from caudate nucleus and putamen to the globus pallidus, thence viâ the thalamic fasciculus to the thalamus, whence they are relayed on to the cortex; or after leaving the globus pallidus they may pass in the ansa lenticularis and so reach the cortex viâ the red nucleus or the corpus subthalamicum and thalamus.

Wilson is evidently convinced that impulses from the corpus striatum reach the cortex even if by an indirect route, for he says in his paper on progressive lenticular degeneration, when discussing the probable cause of tremor: "It is conceivable, however, that the absence of the normal steadying influence of the lenticular nucleus may make itself felt viâ the strio-thalamic fibres on the external parts of the optic thalamus and so on the intermedio-precentral and precentral cortex." Weston Hurst in 1926 showed that the vessel walls in the globus pallidus in fifty out of a hundred cases of chronic nervous disease were infiltrated with iron salts. Barton White published the results of his investigations in thirty cases of mental disorder,

showing a percentage of fifty-four with similar changes in the vessel walls. Hadfield examined the brains of thirty-two cases dying either from accidents or ordinary diseases not associated with mental or chronic nervous disorder, with a similar result, and says "that pallidal siderosis is probably the expression of a slow evolutionary atrophy, affecting the nuclei in at least 60 per cent. of people over the age of thirty."

The palæo-striate body is developed from the rhinencephalon; it contains large, probably motor cells, and its fibres myelinate before those of the neo-striate body.

From all this it appears probable that the globus pallidus is the ganglion in which those reflex actions originate (through the association of sensory impulses, chiefly visual and somatic, with the motor cells) which are necessary for the preservation of the species either by escape from enemies or by obtaining of food, these movements being purely reflex. But in animals with a more highly-developed consciousness, in whom after the first few months of life ideas are formed by the association of the other senses with the muscle sense and consequent stimulation of the sensori-motor cells, ideas which have to be transformed into actions many times before the corresponding reflexes are established, this palæo-striate body is only of use before this higher consciousness has developed, *i.e.* in the early part of their existence, chiefly for such reflex movements as sucking, feeding and swallowing. Later, when the putamen and caudate nucleus have become the centres for muscle-sense associations the palæo-striate body gradually deteriorates, and is used chiefly as a passage for the impulses which originate in these later developed nuclei to the cortex and other parts of the central nervous system. The fact that the neo-striate body, consisting of the putamen and caudate nucleus,

is developed later, both phylogenetically and ontogenetically, appears to support this view.

As to the various mental states of the epileptic before and immediately following the seizures, also his temperament in the intervals, are these the consequences or merely the concomitants of the fits? That they are due directly to the seizures appears the more probable, for in other forms of epilepsy, migraine, etc., states of mental alienation do not appear to be more frequent than in the non-epileptic part of the community, and, contrary to what was thought at one time, states of acute mental trouble are not as common following *petit mal* as they are in those who suffer from the major attack. In fact, it is rare for a patient to be admitted to an asylum suffering only from the former: although, in the history of those who have had to be placed under restraint, it often transpires that they have suffered from attacks of *petit mal* for some years before the major seizures commenced, and that, as a rule, these attacks have continued at intervals for a considerable period before the mental state has necessitated the removal of the patient to an institution. What, then, is the probable explanation?

Bevan Lewis, in his text-book of mental diseases, when speaking of states of mental depression, points out very clearly that our ideas of the space attributes of the body are dependent largely on our sixth or muscular sense. He explains that the muscle sense concerned in these concepts is derived chiefly from the movement of the eyes, that the sense of these muscular contractions lapses eventually in consciousness as a pure muscular sensation, and that in states of mental depression this sense which has lapsed rises again into consciousness, giving rise to a feeling of effort which

(being unusual) at once suggests to the mind the notion of resistance, and so engenders ideas of suspicion and persecution. According to this author the muscular sense is the fundamental element of thought.

If those sensori-motor cells, the stimulation of which, as Dr. Hughlings Jackson suggests, gives rise to our ideas, are being constantly irritated by stimuli reaching them from an unstable centre, they will be maintained in a state of constant hypertension, ready to act too quickly, and this condition may easily account for the extreme irritability and impulsive conduct of epileptics in the intervals between their seizures.

Owing to the increased stimuli arising a short time before the fit, they will be in a state of still greater tension, and the conduct will become altered in consequence, giving rise to those conditions of sub-acute mania, increased suspicion with delusions, and sullen, dangerous moroseness so commonly met with at that time, so that their condition between, before and during the fits will be accounted for by the excessive irritation of these sensori-motor cells by impulses arising from an unstable ganglion (which, I submit, is the neo-striate body).

Hughlings Jackson has explained very clearly that the conditions of acute mania, stupor, automatism and semi-coma immediately following the seizures are to be explained as due to the temporary paralysis in varying degree of these same cells, due to exhaustion by the excessive discharge.

Can all this have any bearing on the treatment of the disease ? The various parts of the nervous system are very selective in their choice of drugs. Those which have been our stock remedies in epilepsy have been the bromides, which apparently act directly on the cortical cells, depressing their activity and so

rendering them less liable to discharge. If drugs can be found (I believe luminal to be one) which act directly on the basal ganglia, reducing their irritability, the unwonted and excessive impulses which originate there in epileptics will be reduced or stopped, so relieving the cortex from their excessive irritation. By these means the seizures may be reduced in number and strength, the mental condition improved, as, indeed, we find so frequently the case, and it will be unnecessary to depress our patients with the bromides, which, to be of any use, must be given in large doses, with the result that the appetite is affected, skin eruptions produced, and that highly-developed, though most unstable organ, the cortex, caused to deteriorate and "a desolation created which we call peace."

To sum up. From the evidence before us, clinical, anatomical and psychological, it would appear that :—

1. Ordinary *grand mal* is produced by impulses which arise in the neo-striate body and act upon the cortex.

2. The mental condition of epileptics immediately preceding and in the intervals between the seizures is due to irritation of cortical sensori-motor cells by impulses originating in the striate body.

3. The neo-striate body, consisting of the putamen and caudate nucleus, is the centre for the association of the muscle sense with the other senses.

And as a corollary that—

4. Drugs which act primarily on the basal ganglia in epilepsy are to be preferred to those which act directly on the cortex, as being more efficient and less likely to damage the more highly-developed but less definitely organized cortical cells.

# FIVE YEARS' EXPERIENCE OF SURGERY IN EXOPHTHALMIC GOITRE.*

BY

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UNTIL a few years ago the treatment of exophthalmic goitre was in a very unsatisfactory position. The cases seemed to differ from one another in a puzzling manner. Various enthusiasts held a brief for some line or other of medical or X-ray treatment, and could point to a few remarkable successes which sustained their zeal, but a dispassionate inquiry revealed many failures. The two main indubitable factors in bringing about recovery were rest and time, but often the time was long and the result uncertain. Surgery also achieved some spectacular successes, but there were many half-cures and numerous dreadful disasters. Patients died on the table, or succumbed to hemorrhage or suffocation four or five hours afterwards, or passed into a condition of fatal hyperthyroidism with very high temperature, uncountable pulse, pitiable excitement, and a tremor that shook the bed. Of 23 cases treated surgically before the war at Guy's and St. Thomas's Hospitals, one-third died, another third were no better, and only one or two were really symptom-free. Even when, encouraged by the successful series published by Kocher and the Mayo Clinic, better surgery gave

* Paper read at a meeting of the Bath and Bristol Branch of the British Medical Association, 28th May, 1930.

better results, we were warned not to touch patients with glycosuria or auricular fibrillation.

The general results obtained by medical treatment may be judged by the excellent analyses published by Hale White and by Williamson and Mackenzie :—

RESULTS OF MEDICAL TREATMENT OF EXOPHTHALMIC GOITRE.

| | Total cases. | Died in hospital. Per cent. | Total. | Cured. Per cent. | Much better. Per cent. | Better. Per cent. | No better. Per cent. | Died since. Per cent. |
|---|---|---|---|---|---|---|---|---|
| 1. Hale White's cases (hospital) .. .. | 161 | 11 | 48 | 54 | — | 25 | 5 | 16 |
| 2. Hale White's cases (private) .. .. | 55 | 0 | 54 | 60 | — | 17 | 6 | 13 |
| 3. Williamson and Mackenzie .. | 56 | 0 | 56 | 18 | 20 | 30 | 8 | 24 |

It will be observed that roughly about half the cases got well, a quarter were better, 6 per cent. not improved, and the mortality was double that of women of the same age in the general community. At the best the progress is tedious, six to eighteen months being a very ordinary time for restoration to fair health, but many cases drag on for years. I have seen them after eleven and even eighteen years. The course is apt to be progressively downwards for a few months, then gradual improvement takes place, which may or may not go on to recovery. The best indication of progress, good or ill, is the body weight. If it is rising there is general improvement, and *vice versa*.

Whether medical treatment at the present day has improved on these results it is for the physicians to say, but I take leave to doubt it. Probably I do not see the

cases that get well quickly; perhaps some do. I see plenty that have dragged on a semi-invalid existence for years, and I know of several that have died of the disease before operation was decided upon.

An important step forward was taken when Plummer, in America, drew a distinction between the different types of thyroid intoxication. It is true that all intermediate grades between two extremes may be met with, and there is sometimes room for difference of opinion as to what a particular case should be labelled, but the differentiation into types is nevertheless of real value. The first type is classical exophthalmic goitre, called *primary thyroid intoxication* by Dunhill. The patient is usually a woman between 20 and 45 (though I have at the present time a girl of 9 and a man of 60 under treatment). The thyroid is enlarged more or less uniformly, and does not contain rounded nodules; exophthalmos is present. These signs, together with the well-known symptoms of nervousness, excitability, tachycardia, fine tremor of the hands, and loss of flesh, all come on together. The goitre may be soft, but in old cases it is hard; it may be very vascular and pulsating; sometimes the thyroid is scarcely at all enlarged.

At the other extreme we see patients usually past 40 with a history of enlarged thyroid for many years, and on palpation we find one or more rounded adenomatous nodules in the gland. At operation some of these are found to be breaking down, partially fluid, or containing a colloid material. The symptoms of thyroid intoxication are just like those of classical exophthalmic goitre, but they have developed comparatively recently, long after the patient knew she had a goitre. Exophthalmos, however, is absent. The nodule in the thyroid may be so small that it can

only be found by careful search, if at all. These cases are usually called "toxic adenoma." Dunhill classifies them as *secondary thyroid intoxication*. He believes that the source of the thyroid intoxication, whether primary or secondary, is to be found in some stimulus brought to the gland, which may be psychical from some emotional upset, or may be septic, the original focus being found in the teeth, tonsils or elsewhere, or else it may be a febrile illness such as influenza. If the stimulus falls on a thyroid gland previously normal the result is primary thyroid intoxication or classical exophthalmic goitre. If the thyroid already contains adenomata, a secondary thyroid intoxication results. It is quite true that psychical, febrile or septic stimuli may make a case of Graves' disease worse, or cause a latent case to become obvious, and removal of the same will often benefit the patient, up to a point, but this theory scarcely seems to do justice to the fact that removal of a single degenerated adenoma will often cure the symptoms. Also, patients with thyroid intoxication are no more subject to psychical, septic or febrile upsets than the general community.

In the present address I have rather loosely grouped all cases of thyroid intoxication together under the title of exophthalmic goitre, as being more familiar to English ears. Cases of non-toxic parenchymatous, adenomatous or malignant goitre are not included.

This classification has a real clinical value, not annulled by the fact that intermediate grades are frequently seen. Classical exophthalmic goitre, primary thyroid intoxication, has a definite tendency in about half the cases to get well. As a rule, and for a brief period, it is favourably influenced by rest in bed, and the administration of Lugol's iodine, ten drops twice

a day. It is true that the benefit soon wears off, and it is probably best to keep it in reserve for the week or two previous to an operation, when the effect may be very striking and valuable.

Toxic adenoma has no tendency to get well, and is but little improved by iodine or other remedies; it is likely to go on to permanent damage to the cardiac muscle with auricular fibrillation. Glycosuria may be seen with either type of thyroid intoxication; so may mental changes. Toxic adenoma ought always to be operated on, the presence of auricular fibrillation or glycosuria making the indications for removal not less but more urgent, and the risks of operation are very small, if the heart is not yet gravely diseased.

The proper place for surgery in classical exophthalmic goitre is not so easy to allocate. Five years ago we made it a rule to allow twelve months from the onset of symptoms before advising operation. During that year medical or X-ray treatment should be given an opportunity to effect a cure. Lately, encouraged by experience of the safety of operation and the practical certainty of benefit, we have been offering, if not advising, surgical treatment to quite early cases. Take, for example, a young woman earning her own living, seen recently, with symptoms of Graves' disease for three months, getting worse. Which shall we offer her, a year's rest, with only a 50 per cent. chance at the end of that time of being well enough to do her work, or an operation, that holds out good prospect of making her fit in, say, two months? It is not surprising that she, her relatives, and her doctor chose the latter, and she is doing very well.

We turn, then, to the question of the risks and benefits of surgery to-day for thyroid intoxication. Dunhill, with his immense experience, reports a

mortality of only 2·7 per cent. Even of 100 cases of auricular fibrillation only 9 per cent. died. Regular rhythm returned in 48 patients spontaneously, and in 32 more with the aid of quinidine.

During the past five years I have operated 62 times on 52 patients for classical exophthalmic goitre or for toxic adenoma. There have been, of course, a number of operations for ordinary adenomatous or parenchymatous goitre besides. The patients had been ill for over a year in all cases, except one just mentioned, and often for many years. Four patients died in hospital. One of these was very ill with auricular fibrillation, and operation was rather a forlorn hope. She died next day, and the post-mortem showed broncho-pneumonia and a fatty liver. Another survived ten days, but finally succumbed, and was found to have abscesses of the kidney, the culture from which showed *B. coli*. Both these cases may be regarded as marked for death anyhow. The others died of reactionary hemorrhage, a risk which can be practically eliminated by the measures we are now taking against it. More than half the cases were of classical exophthalmic goitre.

The procedure adopted has been as follows. The patient is kept in bed in the nursing home or hospital for at least a week. During this time Dr. Herapath has usually seen them, and often an electrocardiogram has been taken. In cases of the classical Graves' disease type Lugol's iodine is given. The anæsthetic has been given in practically all my cases by Dr. L. A. Moore. It has usually been open ether, but in our last eight or ten cases we have used avertin and a local anæsthetic, with or without a drachm or two of ether. To obtain a real cure it is necessary in cases of toxic adenoma to remove the degenerating nodules, and in exophthalmic goitre to take away five-sixths of the total gland

substance. Sometimes this can be done safely at one operation. More frequently it is better to content oneself with a hemi-thyroidectomy, and to remove part of the remaining lobe about three months later, when the patient is likely to be greatly improved. In one case it was thought best at the first intervention merely to tie the superior thyroid arteries. The steps of the operation are as follows: A collar incision is made, with reflection of muscles and fascia to expose the goitre. The superior thyroid artery is ligatured and re-ligatured. The corresponding lobe of the thyroid gland is enucleated. Then the branches of the inferior thyroid artery are ligatured and re-ligatured close to the gland, and the goitre is resected on that side, leaving a portion at the back and adjacent to the trachea. The raw surface is infolded and sutured, all small vessels are transfixed and tied, and the patient is allowed to come round to cough and strain, so as to demonstrate hæmostasis; the wound is then sewn up with a stab drain. A special nurse is in charge for twelve hours. After that time has elapsed the risks are almost past.

Ill consequences are unusual. I have not seen tetany follow. A few cases have had weakness of the voice from recurrent laryngeal nerve palsy; this has more than once come on late, and seems to be due to involvement in scar tissue, not section. Three patients have had fatal illnesses months after apparent recovery, and probably due to some intercurrent disease. One patient suffering from chronic insomnia was greatly benefited physically, but the result was largely spoiled by the persistent inability to sleep. Another, an old man, did well for years, then became insane. As far as I know, all the rest are either quite symptom-free, or well enough to lead a more or less normal life.

Some are not perfect, because having had a hemi-thyroidectomy, they are so well that they did not desire a second operation. Cure is merely a question of removing enough thyroid. The pulse-rate usually returns to normal about ten days after the operation.

As Walton has pointed out, these patients suffer badly from heat, and it is not wise to operate during the few weeks of really hot weather that we usually get in July.

Patients with a thyroid adenoma ought not to be left until degeneration giving rise to toxic symptoms has set in. By removal at an earlier period this risk, and that of malignancy, can and ought to be avoided.

To sum up, in our opinion all cases of toxic adenoma of the thyroid should be operated on, and all cases of classical exophthalmic goitre after a year's duration, unless mentally deranged. There is a good deal of reason for operating also in early cases. Auricular fibrillation and glycosuria will probably clear up after subtotal thyroidectomy.

# THE TREATMENT OF GRAVES' DISEASE.*

BY

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Five years ago I was of the opinion that the treatment of Graves' disease by operation was barely justifiable, but at the same time I was profoundly disappointed with the results of treatment by medical means. All the usual remedies had been tried—rest in bed for long periods, bromides, belladonna, sodium phosphate, iodine in large doses, and in small doses very frequently repeated, pancreas, insulin and deep X-rays—but the results were poor. In many cases there was improvement for a time, but the cases usually relapsed after a while, and the ground gained was lost in a short period; in other cases medical treatment seemed to do no good at all. The eradication of septic foci has long been advised and has been tried. For instance, in one case, that of a woman with pronounced Graves' disease, the teeth were very septic and a dentist was asked to clear the mouth. This was followed by a marked improvement, the thyroid became almost normal in size, the tachycardia quieted down and she gained a stone in weight. Six months later she returned to out-patients, and was just as bad as she was when first seen. Graves' disease is one of those conditions which may have marked remissions, and very often a remission has been taken to be the result of treatment.

When Mr. Short began his work on goitres he kindly asked me to see all his cases at the Bristol

* Paper read at a meeting of the Bath and Bristol Branch of the British Medical Association, 28th May, 1930.

Royal Infirmary, so that I might watch the results of operation. It was my custom to see them before and then again after the operation; and if this was done in more than one stage, I saw them after each stage.

It is obvious that one of the best methods of demonstrating the effects of treatment is by an electrocardiogram. Lead 1 is taken from the two hands, and therefore shows the amount of tremor present. The amount of tachycardia is well seen in all leads, and any irregularity of the heart such as auricular fibrillation can be shown. Willius, in analysing 500 consecutive cases of this irregularity, found that Graves' disease was responsible for 27·9 per cent. and toxic adenoma of the thyroid for 20·5 per cent. of cases, which shows what an important factor the thyroid is in the production of auricular fibrillation. Records of 45 cases have been taken, but as only a few cases can be quoted here, I have selected 5 to show various points.

**Case 1.**—S. B., a woman with severe Graves' disease, had a marked tremor and a pulse-rate of 141. (Fig. 1.) Six months after operation she showed practically no tremor, and her pulse-rate had come down to 85. (Fig. 2.)

**Case 2.**—E. C., a woman who had had Graves' disease for eleven years, had been treated by me for three years with no improvement. At the end of this time she had tremor, tachycardia of 140, marked emaciation, and she was a nervous wreck. She was operated upon in two stages, and after six months the tremor was almost gone, her pulse-rate was 93, her nervousness was much improved, and she had put on a lot of weight; in fact, when she came to see me I did not recognize her; she looked a different woman. (Figs. 3 and 4.)

**Case 3.**—G. G. was a man who had been treated for twelve months in Australia for Graves' disease. They had tried every method of treatment, short of operation, and in the end they told him that they could do nothing more for him, so he returned to England. When I saw him he was a very

# PLATE V.

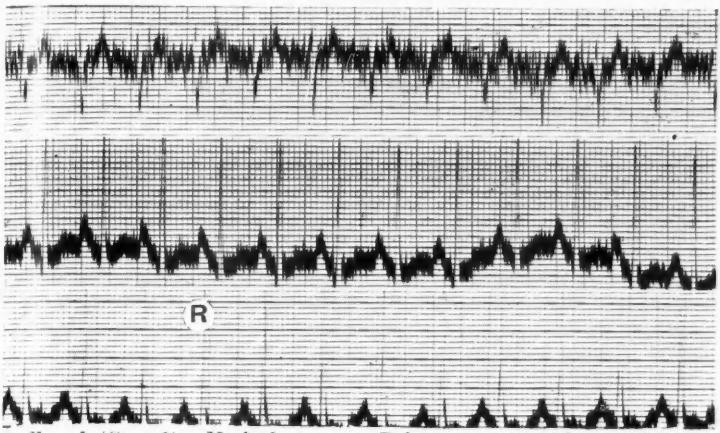


FIG. 1 (Case 1).—Marked tremor. Pulse rate 141. R's very high.

FIG. 2 (Case 1).—Six months after operation, tremor slight. Pulse rate 85. R's much smaller.

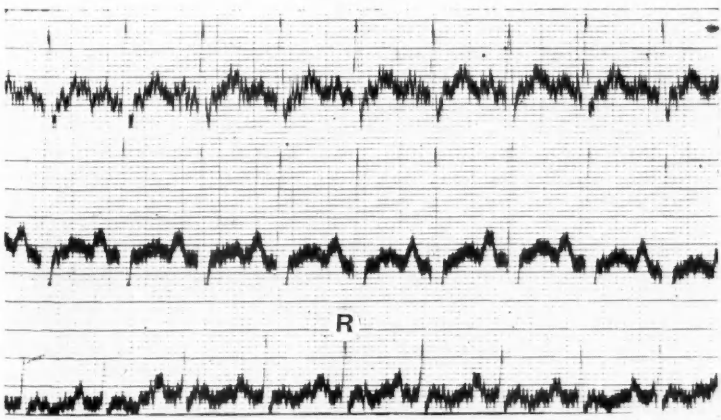


FIG. 3 (Case 2).—Pulse rate 140. Tremor marked. R's high.

# PLATE VI.

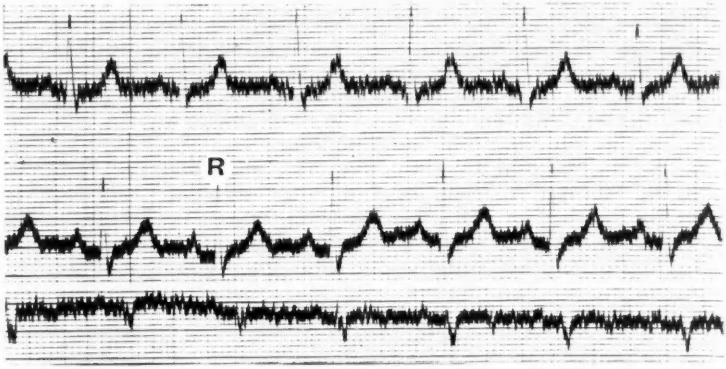


FIG. 4 (Case 2).—Pulse rate 93. Six months after operation. R's smaller. Lead III., altered.

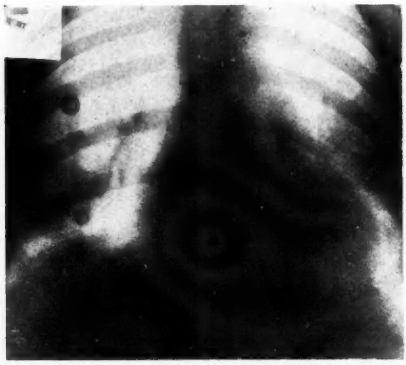

FIG. 5 (Case 3).—Transverse diameter 16·1 cm. 30th January, 1928.

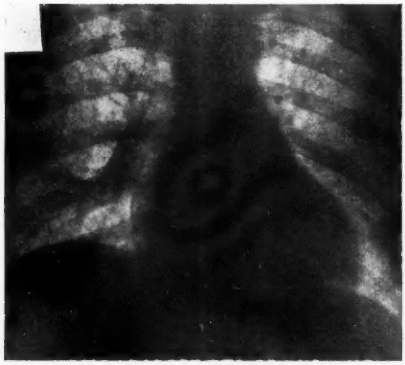

FIG. 6 (Case 3).—Transverse diameter 14·7 cm. 25th June, 1928.

# PLATE VII.

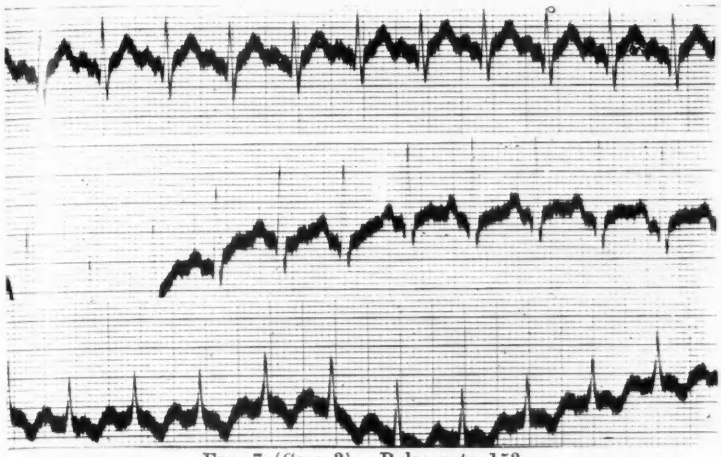

FIG. 7 (Case 3).—Pulse rate 153.

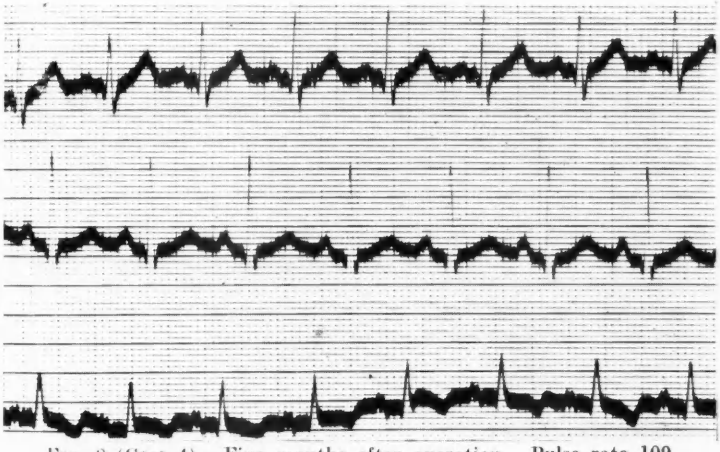

FIG. 8 (Case 4).—Five months after operation. Pulse rate 109.

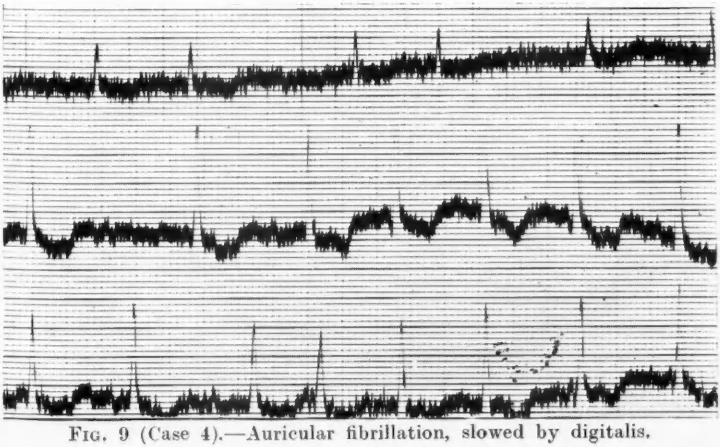

FIG. 9 (Case 4).—Auricular fibrillation, slowed by digitalis.

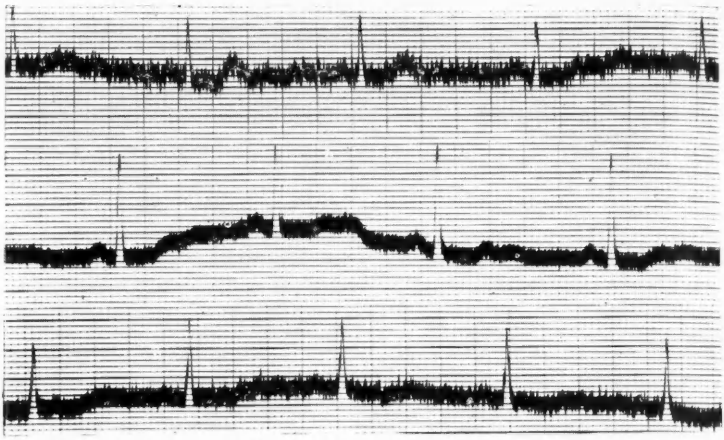

FIG. 10 (Case 4).—Three weeks after operation, normal rhythm.

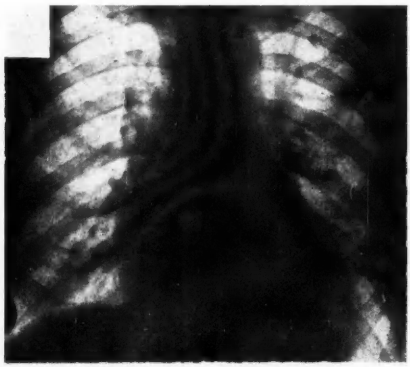

FIG. 11 (Case 5).—Transverse diameter 15·7 cm. 16th September, 1929.

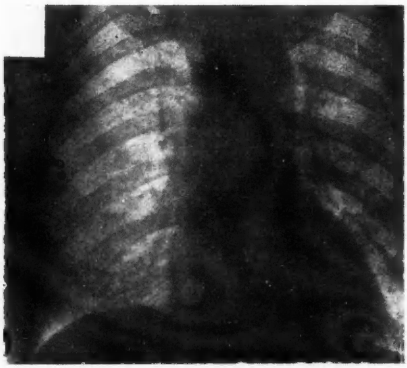

FIG. 12 (Case 5).—Transverse diameter 13·5 cm. 15th November, 1929.

# PLATE IX.

FIG. 13.—Auricular fibrillation, slowed by digitalis.

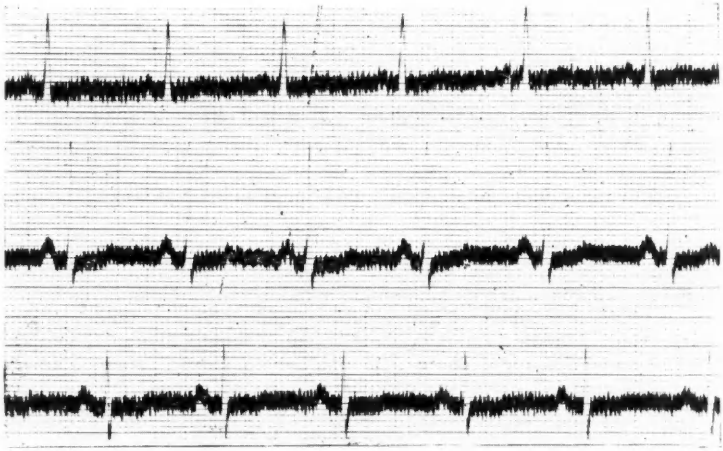

FIG. 14.—Two months after operation. Normal rhythm. Rate 75.

severe case with marked exophthalmos, tremor, and a pulse-rate of 153. The heart was enlarged, but regular, and there were no murmurs. An X-ray film was taken at 7 feet from the tube to show the size of the heart (Fig. 5), and the transverse diameter of the heart was 16·1 cm. His electrocardiogram is shown in Fig. 7. His operation was done in June, 1928, and five months afterwards the pulse-rate was 109 (Fig. 8), and the transverse diameter of the heart had decreased to 14·7 cm. (Fig. 6.) I saw him again in May, 1930, when his pulse-rate was 88 and the heart was the same size. He had neither exophthalmos nor tremor, and he felt and looked a perfectly fit man.

**Case 4** is one in which I was associated with Mr. C. Ferrier Walters. It was that of a woman who had a toxic adenoma of the thyroid, and rapid, irregular heart characteristic of auricular fibrillation. She complained of shortness of breath, but had no objective signs of congestive heart failure. Digitalis was given till the heart-rate was slowed, and then the adenoma was removed. Three weeks later she was noted to have a regular pulse, and an electrocardiogram showed that her rhythm had become normal. (Figs. 9 and 10.) The operation was in August, 1927; she came up for examination in May, 1930, and her rhythm was found to be still normal. She is no longer short of breath, and is doing all her home work.

**Case 5** was a man of good physique who was sent up by Dr. Bernard because he had been turned down for a good railway job on account of his heart. On examination he was found to have auricular fibrillation with no murmurs, and X-rays showed the transverse diameter of the heart was 15·7 cm. (Fig. 11.) He had a small adenoma of the thyroid with some tremor. He was admitted, after some delay while he was considering the question of operation. When Mr. Short saw him the adenoma was so small that it was hard to perceive, but it was found and operation was agreed upon. The heart was first slowed by digitalis and then the adenoma removed. The fibrillation, however, persisted, so after two months he was given quinidine. This was given in doses of 0·4 grams every two hours, and after the fourth dose his rhythm changed and became regular. After nine days an electrocardiogram was taken. (Figs. 13 and 14.) The pulse-rate was now 75. An X-ray film was taken, and the heart's transverse diameter was 13·5 cm. (Fig. 12.) He was examined again in April, 1930, five months later, and he informed me that he had now passed the doctor, obtained his job, and felt perfectly fit.

We have met with two cases in which glycosuria was present. In one of these there were all the symptoms of diabetes in addition, and ketones were present in the urine. She was given 25 units of insulin, covered with an ounce of glucose, previous to the operation. She did perfectly well, and since the operation the glycosuria has disappeared, with all the other symptoms of diabetes.

The results of operation in these 45 cases have impressed me very much as to the certainty of relief, provided enough of the thyroid is removed during the operation. It is well known that the result of medical treatment is uncertain, and it seems to me to be debatable whether it is fair to submit a case to prolonged treatment by medical means when the issue is in doubt.

One knows that operation will relieve, but of course there is a certain risk during that operation, though the risk is getting less and less, thanks to improvement in the technique of the surgeons. My own impression is that in an early case of Graves' disease a chance should be given to medical treatment, but that if no improvement is shown in six months the question of operation should be seriously considered. In a case of well-established Graves' disease operation should be proceeded with at once. If auricular fibrillation has supervened operation is the more certainly needed, for operation is the only means of removing the factor by which this condition is caused. If this factor be removed there should be no recurrence of the abnormal rhythm, whereas as long as the irregularity persists the patients are condemned to be chronic invalids. In cases where there is an adenoma of the thyroid, this should be removed by operation as soon as symptoms arise.

# CHANGES IN THE SPLEEN IN ACUTE PYOGENIC INFECTIONS. *

BY

T. F. R. HEWER, M.D.,

*Commonwealth Fund Fellow.*

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THE enlargement of the spleen in acute infections has long been recognized by clinicians and pathologists alike. In typhoid fever, malaria and in all pyogenic infections one expects to find a palpable spleen. The typhoid spleen is seen at post-mortem to be an almost fluid mass of a deep red colour; its increased size is due to the enormous number of red-blood corpuscles in the sinuses and in the pulp, and on section one sees many phagocytic cells, some of which are endothelial cells from the splenic venules, while others are macrophages similar to those found elsewhere: there are only a few nucleated cells in such a pulp, and if the hæmoglobin be washed out by fixation in alcohol the tissue looks rarefied under the microscope. Such changes as these are entirely different from those to be discussed in this paper, and the splenomegaly of protozoal diseases will not be considered.

In practically all acute pyogenic infections, but especially in septicæmias, the spleen becomes tumefied, so that it is readily palpable beneath the costal

* A thesis presented for the degree of M.D. in the University of Bristol.

margin. Its general appearance has been described by MacCallum,[1] and the following is taken from his account. Its size varies greatly, but its weight, in adults, may reach 600 or 700 grams or more. The capsule is tense, but the organ is soft, so that when it is cut the surface swells forward, everting the edges of the capsule. One may scrape off with the knife a quantity of smeary, paint-like pulp. The spleen may even be so soft that it flows as a semi-fluid material. The trabeculæ are sunken below the swollen surface, or else, if the cut surface has been scraped, they alone may be left as shaggy threads after the pulp has been wiped away to a considerable depth. In such extreme examples it is difficult even to see the Malpighian bodies, but in some cases they are much enlarged and conspicuous, sometimes with an opaque, yellowish, central fleck in each. Ordinarily the splenic pulp in such swollen spleens has a velvety or pasty appearance, and is very opaque and of a dull, pinkish-grey colour.

It must not be imagined that this advanced change is the rule. In a survey of a few hundred cases in the autopsy records of the Johns Hopkins Hospital I found an infinite variation in the degree of gross change. In many instances a note had been made to the effect that the spleen did not seem to be enlarged and had not the appearance of an "acute splenic tumour," but in some of these there were quite definite microscopical changes similar to those seen in the more pronounced cases.

Before describing the microscopical changes in such spleens it will be necessary to say something about the normal histology of the spleen as it was worked out by Weidenreich[2] and Mollier.[3] The Malpighian bodies are collections of lymphoid cells lying in a

reticulum formed from the adventitia of arterioles. After leaving the Malpighian bodies the branches of these arterioles empty each into one of the wide venules which make up the bulk of the splenic pulp. The walls of these venules are formed of elongated endothelial cells whose central nucleus is large, and causes a bulging at the middle point of the cell, which projects into the lumen of the venule. Outside these endothelial cells there is a reticulum of elastic fibrils connecting with the general reticulum of the pulp. Weidenreich states that there is also an intervening structureless basement membrane. In the spaces between the venules there lie the cells of the splenic pulp, about which we know least and are, in this paper, most concerned. Many red cells and various mononuclear cells are normally found there; polymorphonuclear leucocytes are present in small numbers. The question as to whether any of the mononuclear cells are peculiar to the spleen or whether they contribute at all to the circulating blood is an open one. There seems to be no doubt that in such conditions as osteosclerotic anæmia, resulting from tumour metastases in the marrow-cavity of long bones, myelocytes can be formed in the splenic pulp, giving it some of the characteristics of bone marrow. It is also certain that some of the mononuclear cells of the pulp are phagocytic; the endothelial cells of the venules and some of the large reticulum cells are often found laden with pigment.

Various authors, such as Evans,[4] Kozumi[5] and Goldzieher,[6] have attempted to classify different types and degrees of splenic change in acute bacterial infections on an elaborate ætiological basis; but the only divisions for which there seems to be any justification are the "red" and "grey" types, the

former occurring in typhoid, and the latter in the pyogenic infections which we shall consider.

In a microscopical study of these spleens one can see with the low power (Fig. 1) that there is a great increase in the number of cells in the pulp, so that the sinuses are compressed and, in the more advanced cases, almost empty of blood.

In some of the more extreme cases it is practically impossible to distinguish the outline of the sinus walls, and it looks as if there were an actual solution of the supporting reticulum; this has been described by Goldzieher,[6] who suggests that damage to the reticulum fibrils accounts for the softness and friability of the spleen. But similar damage to the reticulum was seen in some of my experimental animals which died during the night, and in these there were no other alterations in the spleen, while freshly-fixed "acute splenic tumours" did not show such changes; thus it is possible that a large part of the change in the reticulum is due to post-mortem autolysis.

By examination under a higher power one can see that the increased cellularity of the pulp results from the summation of many factors. There is some proliferation of the endothelium lining the sinuses; whether this is a regenerative process following damage to the original endothelium or merely a preparation for increased activity of the spleen it is difficult to say. Phagocytosis is not a prominent feature. Proliferation of the reticulum is not apparent except, perhaps, in cases where there has been a long-standing sub-acute infection. In the pulp between the walls of the sinuses there is a variable number of polymorphonuclear leucocytes, and, most noticeable of all, an infinite variety of mononuclear cells. The Malpighian bodies show almost as great a diversity of

# PLATE X.

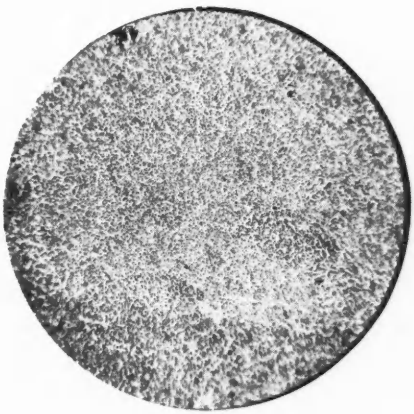

FIG. 1.

(Low power.) Spleen from a case of general peritonitis. Note increased cellularity of pulp and a ragged follicle.

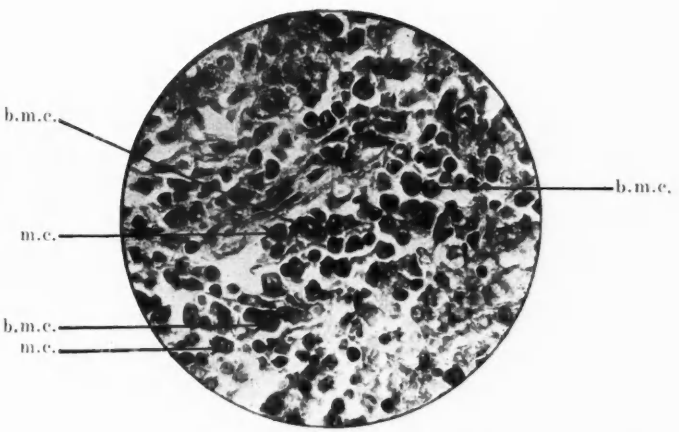


FIG. 2.

(Oil immersion.) Same section as Fig. 1. Note large basophil mononuclear cells, b.m.c., and smaller myeloid cells, m.c.

change as does the pulp. In some instances, more particularly in children, they are greatly enlarged, and the "germinal centres" are considerably hypertrophied, often, apparently, at the expense of the surrounding zone of lymphocytes. It is this change in the centre which produces the gross appearance of yellowish central flecks. The cells accountable for this alteration have abundant pale-staining, non-granular cytoplasm and a large round nucleus with rather scanty chromatin and one or two small nucleoli. Such cells are also found towards the periphery of the follicle and occasionally in the adjoining pulp; they have been described by Washkewitz[1 2] as peculiar to diphtheria, but they are found equally commonly in other infections, especially in young people. Rather more frequently the Malpighian bodies are ragged, without any proliferation of the "germinal centres," and many of the lymphocytes are pyknotic and being phagocytosed by wandering cells; they may even appear like focal necroses.

Examination under oil-immersion enables one to differentiate the mononuclear cells of the pulp in this condition into at least four groups (Fig. 2):—

(*a*) Lymphocytes, similar to those in the follicles and in the blood-stream.

(*b*) Small plasma cells which have the characteristic appearance when stained with the Unna-Pappenheim methyl-green-pyronin stain or with eosin-methylene-blue.

(*c*) Myelocytes, neutrophil and eosinophil, whose granules are well seen with Wright's stain.

(*d*) A large group of cells with a granular but basophil cytoplasm, whose size varies from that of the ordinary myelocytes up to the large cells, which are

clearly seen under low power, with a diameter about twice that of a normal myelocyte.

These last cells are described by Huebschmann,[7] Kozumi[5] and others as plasma-cells; they refer to the largest cells as "lymphoblastic" plasma-cells. Huebschmann admits that they do not give the typical staining reaction of plasma-cells, particularly in that there is no peri-nuclear halo; the cells to which he refers are well illustrated in his paper and are identical with the ones we are considering. He mentions the large "lymphoblastic plasma-cells" inside the lymphoid follicles, and remarks that their cytoplasm is paler than that of the cells in the pulp. The nuclei of those cells in the follicles are practically identical with those of the large cells in the pulp; in each case the nuclear material is rather loosely arranged, and there are from one to three nucleoli; there is no suggestion in any of these cells of the typical wheel-spoke arrangement found in plasma-cells.

Goldzieher suggests that these large basophil cells in the pulp may arise from sinus endothelium, because he has observed developing basophilia of the lining endothelium and desquamation of these cells into the sinuses. One is inclined to doubt the truth of this suggestion, because these endothelials are smaller and most of the cells we are considering appear in the pulp between the sinuses.

As early as 1900 Dominici[8] described these large basophil cells in the spleen in acute infections. He noticed that they were of different sizes and thought them lymphoblastic; he differentiated them from true plasma-cells which, he said, were also present but in smaller numbers. In long-continued infections he found they are apparently changed into basophil myelocytes.

Ziegler[9] describes similar cells in the spleen in myeloid leukæmia and considers them myeloblastic. Schridde[10] states that the changes in acute splenic tumour represent a myeloblastic reaction, and sees the same large mononuclear cells in myeloid leukæmia ; he identifies these with the " large plasma-cells " of other authors and believes them to be myeloblasts. Neither of these authors gives any definite reason for his belief. The work reported in this paper represents an attempt to prove or disprove these views.

I find many of the smaller basophil mononuclear cells very like myelocytes, and with a Wright's stain a few fine granules are seen in the cytoplasm. When the larger cells are undergoing mitosis one also finds granules in the cytoplasm.

An oxydase stain of such a spleen shows a considerable increase of oxydase-positive cells. Great difficulty has been experienced in accurately identifying the cells which give this reaction because of the manner in which the granules obscure the nucleus. I found it more satisfactory to stain thin frozen sections with pyronin or safranin and examine them wet, without a cover-slip ; focusing on one cell which could be recognized as one of the large mononuclear cells under discussion and then running on to the slide, still under the microscope, a solution of Winkler's oxydase stain. In this way it was possible to discover which cell reacted. After repeating this procedure on many different cells the conclusion was reached that the oxydase reaction was given by the smaller of the mononuclear cells but not by the very large ones. It was also positive, of course, in the myelocytes, polymorphonuclear leucocytes and in those phagocytic endothelial cells which contained other cell debris. This conclusion 'agrees with the impression that one

gets on examining an ordinary oxydase stain of the spleen in these infections. It is generally accepted that myeloblasts do not give an oxydase reaction; this was worked out by Dunn[13] in a paper on the use of the reaction in the diagnosis of leukæmias. It is equally well known that the more mature cells in the myeloid series, myelocytes and polymorphonuclear leucocytes, do give the reaction; hence these observations led one to think that the whole series might be of myeloblastic origin, particularly as a great similarity is found between many of these cells and the agranular myeloid cells in the bone-marrow.

The microscopical changes described above are those usually encountered in adults. In infants under one year the picture is so different as to require a separate description. There is an increase in size due to increased cellularity of the pulp and, often, increase in the number of cells in the "germinal centres" of the Malpighian bodies, and the gross appearance may not be very different from that of adults, but it is in the nature of the cellular change that the difference lies. There is an increase in the physiological extra-medullary blood formation; one sees numerous myelocytes and some normoblasts. The picture is very similar to that seen in congenital syphilis, where there is an abnormal persistence of the embryonic blood-formation, but in the latter the change is usually rather localized, the normoblasts and myeloid cells appearing in groups in the pulp. It seems that in acute pyogenic infections the cells are more scattered and there are fewer cells of the erythrocyte series. It may be remarked that this state of affairs is found in the absence of any suspicion of congenital syphilis.

The interpretation of these microscopical findings is not easy, as one may judge from the divergent views

of many authors. Jawein[11] regarded the swelling of the spleen as a process associated with the destruction of red corpuscles, and found that it occurred only in those intoxications and infections in which there was much blood destruction; he considers the cellular hyperplasia of the pulp to be purely phagocytic. I rarely saw any erythrophagocytosis worth mentioning in my spleens, and do not agree that the majority of the mononuclear cells exercise any phagocytic action at all. In the typhoid spleen this phagocytic explanation undoubtedly holds. Schridde and Ziegler, as already stated, considered the change myeloblastic in origin. More recently Bykowa[14] published some work on animals which demonstrated the appearance of myeloid cells and what he describes as hypertrophied reticulo-endothelial cells in the splenic pulp after injection with toxins and bacteria. He injected scarlet fever toxin into mice, and when the doses were sub-lethal and repeated he found these changes; similarly he produced myelopoiesis by injection with living diphtheria bacilli together with diphtheria toxin. Similar results were obtained with dogs, myeloid cells appearing in the spleen, liver, lymph nodes and adrenals. He does not appear to have kept any record of the leucocyte count during the experiments. Morris,[15] in 1907, induced anæmia in rabbits with pyrodin and found compensatory hyperplasia of the bone marrow and, in the spleen, large non-granular mononuclear cells like those in the bone marrow, varying in size from that of red cells to more than twice that diameter, and having very basophilic cytoplasm and a paler nucleus. From these large cells he found all gradations down to typical granular myelocytes. Neither Bykowa nor Morris applied these observations to the study of the spleen in acute

infections, but their accounts of the cells they found tally closely with those described above.

In order to investigate more fully the ætiology of the changes in the spleen it was thought advisable to make a detailed study of a number of cases in the autopsy records of acute infections, irrespective of whether they were said to have "acute splenic tumours" or not. I therefore drew up, in tabular form, lists of 180 cases in which full clinical and pathological data were available. It was found possible after prolonged study of these spleens to make a mental estimate of the degree of splenic change by observing the relative number of large mononuclear cells present in the pulp. It is admitted that this involves a large personal factor, but other methods, such as making differential cell counts, although sounding more scientific, are extremely cumbersome and probably no more accurate.

The data collected in these cases were the age of the patient, the nature of the disease, the duration of the disease, the pathogenic organism, the leucocyte count before death, and notes on the examination of the spleen and bone marrow. The age factor was important because, as has been mentioned, there are certain differences in the form of the reaction to infection in infants and young children. It was found impracticable to formulate any relation between the duration of the disease and the degree of splenic alteration, because of the almost invariable presence of a more active phase of the infection at the termination. The nature of the disease was of no statistical importance, a pneumococcal peritonitis producing the same sort of change as a pneumococcal infection of like virulence elsewhere. The most noteworthy results were obtained by a consideration of the degree of

leucocytosis attained before death, and for this purpose it was found advisable to divide the cases into three age groups: those under one year, those between one and five years, and those over five. A summary of the results is given here in tabular form. As one has already mentioned, a mental estimate of the degree of splenic change was made by observing the relative number of large mononuclear cells in the pulp. In these tables "0" means that none of the large cells were present, while one, two, three and four "+" signify an increasing number.

*Under one year old. 65 cases.*

| Degree of splenic change .. .. | 0 | + | ++ | +++ | ++++ |
|---|---|---|---|---|---|
| No. of cases .. .. | 36 | 18 | 9 | 2 | None. |
| Average leucocyte count in thousands | 16·8 | 19·4 | 26·8 | 19·5 | — |

*Between one and five years. 24 cases.*

| Degree of splenic change .. .. | 0 | + | ++ | +++ | ++++ |
|---|---|---|---|---|---|
| No. of cases .. .. | 4 | 4 | 11 | 5 | None. |
| Average leucocyte count in thousands | 20 | 28 | 25·6 | 26·8 | — |

*Over five years. 90 cases.*

| Degree of splenic change .. .. | 0 | + | ++ | +++ | ++++ |
|---|---|---|---|---|---|
| No. of cases .. .. | 8 | 18 | 30 | 32 | 2 |
| Average leucocyte count in thousands | 13 | 14·4 | 20 | 21·5 | 27·5 |

It will be seen from these tables that in infants, while the majority of cases showed no large mononuclear cells in the spleen, those in which they were present had on the whole a higher leucocyte count. In children between the ages of one and five an increasing number had the cells present, and there was a rough agreement between the number of cells and the leucocytosis. In persons over five, however, the results were much more striking. It was found here quite definitely that where there was a high leucocytosis there was also a high degree of splenic change. There were a few rather notable exceptions, which will be discussed later, but even though they were included in these statistics the averages conform with the thesis.

Before one could begin to generalize upon the part played by a demand for leucocytes upon the production of " acute splenic tumour " it was necessary to explore some other possibilities. It was suggested, for instance, that as pyrexia was a factor common to all these infections it was desirable to discover whether an elevated body temperature, in the absence of pyogenic infection, could produce any such changes in the spleen. To investigate this possibility a series of autopsies was collected in which there had been pyrexia as a result of cerebral injury.

Six cases were found where there had been pronounced pyrexia (100°–107°·6) for periods of fourteen hours to seven days, and in none of these was there any change in the spleen. To investigate the question further, pyrexia was produced artificially in rabbits by placing them in an incubator and gradually raising the temperature from that of the room to a maximum of 44° C. The results of these inquiries were that the spleens of six human cases of pyrexia of cerebral

origin were found to show no changes similar to acute splenic tumour, and the spleens of five rabbits whose temperatures were artificially raised in an incubator to points corresponding with those obtaining in the course of acute infections showed no changes. The rabbit spleens were compared with those of six normal controls and with those of at least twenty which had acute pyogenic infections and the usual concomitant reaction in the spleen. It is concluded that pyrexia alone is not responsible for the presence of any of the cells found in acute splenic tumour.

There is one other factor which is common to all infections, and that is the production of antibodies, and since little is known about the actual mechanism of antibody formation it was thought necessary to consider the possibility of a relation between the changes in the splenic pulp with this function, especially as it has been abundantly proved that the spleen is an important organ in this respect. In 1898 Pfeiffer and Marx,[16] working with cholera, found more immune bodies in the spleen and bone marrow than in the blood, and also discovered that while splenectomy does not prevent subsequent immunization, it very greatly diminishes it if the operation be performed just after a course of immunization has been begun. At the same time Wassermann[17] and Wassermann[18] found antibodies demonstrable in the spleen, bone marrow and lymph nodes several days before they could be detected in the blood. Van Emden[19] confirmed this. In 1913 Tsurumi and Kohda[20] injected dogs intravenously with typhoid bacilli and found agglutinins earlier in the spleen than elsewhere; they also noted decreased antibody formation in splenectomized animals. In the same year Przygode[21] grew splenic pulp cells in tissue culture and was able to demonstrate

the production of precipitins and agglutinins when horse serum and typhoid bacilli respectively were added. Schilf,[22] in 1926, found a vibriolysin produced in tissue cultures from the spleen of rabbits and guinea-pigs by the addition of various killed spirochætes. The baneful effects of splenectomy on antibody formation were further demonstrated by Morris and Bullock,[23] and in 1925 Lauda[24] showed that the so-called pernicious anæmia of rats which occurs after splenectomy was the result of a loss of immunity to a latent infection with an organism of the *Bartonella* group.

The following experiments were therefore carried out with a view to determining whether during the active formation of antibodies, in the absence of infection, there appear in the spleen any of the large mononuclear cells found in acute infections. It was decided to use cats for this work, because the normal cat spleen is more like that of man than almost any other laboratory animal, and also the changes occurring in it in acute infections are quite comparable with those seen in man.

Seven normal healthy cats of different ages were killed for controls, complete autopsies performed, and a study made of the spleens and bone marrow. It was found that there were usually a number of small mononuclear cells along the borders of the trabeculæ in the spleen; these are important, in that when a cat died during the night there was a great proliferation of these cells, and care had to be taken to differentiate them from the cells of "acute splenic tumour"; these cells became phagocytic, and possibly played a part in the solution of the reticulum, which has already been mentioned. (Fig. 3.)

Twenty cats were infected with different pyogenic

# PLATE XI.

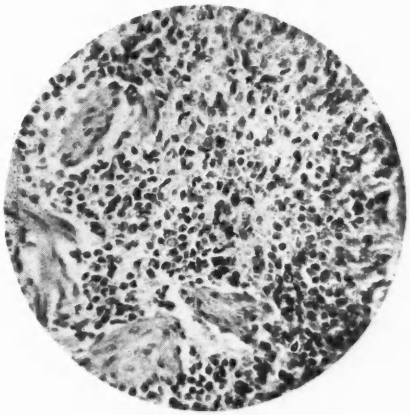

FIG. 3.

(High power.) Normal cat spleen.

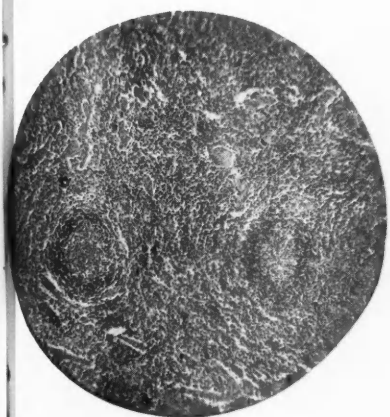

FIG. 4.

(Low power.) Spleen of a cat infected with Staphylococcus aureus. Note cellularity of pulp as in Fig. 1.

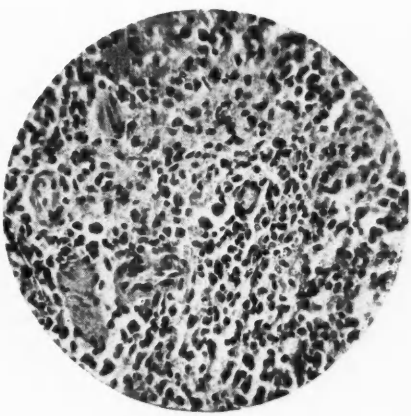

FIG. 5.

(High power.) Same section as Fig. 4. Compare with Fig. 3.

# PLATE XII.

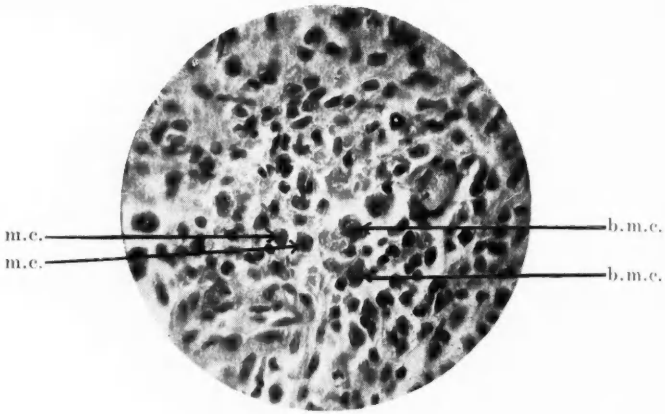


FIG. 6.

(Oil immersion.) Same field as Fig. 5. Compare with Fig. 2. Note large basophil mononuclear cells, b.m.c., and smaller myeloid cells, m.c.

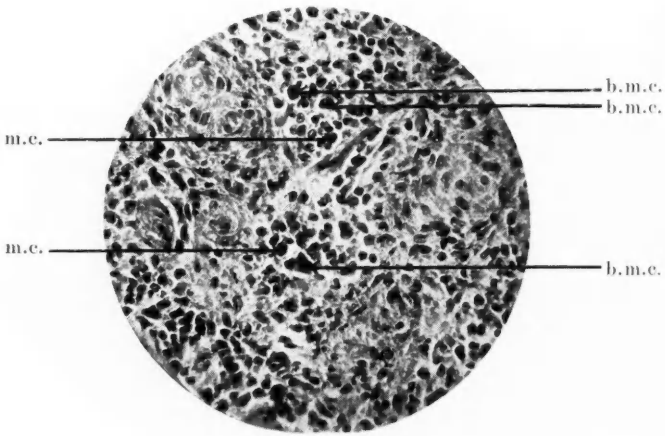


FIG. 7.

(High power.) Spleen of a cat treated with staphylococcus aureus vaccine. Compare with Figs. 3 and 5. Note also the large basophil cells, b.m.c., and smaller myeloid cells, m.c.

organisms by various routes, records kept of their daily temperatures and white cell counts made at intervals. At autopsy sections were made of the spleen and bone marrow and of various other organs involved in the infection. Autopsies were also performed on cats which died of intercurrent infections, such as distemper.

It was found that cats are highly resistant to streptococci. Attempts were made to infect them with cultures of *S. viridans* from a human case of ulcerative endocarditis without effect. Infection with pneumococci was also difficult to obtain. Most of the work was done with staphylococci.

Spleens of twenty cats which had infections with staphylococci and pneumococci, and also those of cats dying of distemper and a few other intercurrent infections, were examined and found to show changes in every way similar to those seen in man. The accompanying microphotographs (Figs. 4, 5 and 6) show the typical large mononuclear cells. The bone marrow was hyperplastic wherever the splenic change was noticeable, and both these alterations corresponded roughly with the degree of leucocytosis developed.

A series of five adult cats were then immunized to diphtheria toxin. Blood serum was taken at the beginning and at the end of the experiment.

1. The first cat of this series was given five doses of toxin-antitoxin (0·5 c.c.) followed by 9 m.l.d. of diphtheria toxin spread over nineteen days. At the end there was paralysis of the hind limbs. The white cell count at the beginning was 12,000 and at the end 11,000.

2. The second cat had four doses of toxin-antitoxin and 29 m.l.d. of diphtheria toxin over a period of

twenty-one days. Paralyses appeared and the cat was killed. The white cell count at the beginning was 13,000 and at the end 11,500.

3. The third cat had five doses of toxin-antitoxin and 124 m.l.d. of diphtheria toxin over a period of twenty-nine days. The last three doses of toxin consisted of 20 m.l.d. on three successive days. There were no paralyses. The white cell count at the beginning was 14,500 and at the end 13,000.

4. The fourth cat had four doses of toxin-antitoxin only over a period of twelve days. The white cell count at the beginning was 14,000 and at the end 15,000.

5. The fifth cat had five doses of toxin-antitoxin and 114 m.l.d. of diphtheria toxin over a period of twenty-nine days, the last three doses consisting each of 20 m.l.d. The white cell count was 15,000 at the beginning and at the end of the experiment.

The diphtheria toxin was standardized immediately before use.

The sera from these cats were injected into guinea-pigs together with lethal doses of diphtheria toxin in corresponding proportions, due consideration being given to the differences in weight of the animals. The sera which were obtained from the cats before treatment with diphtheria toxin exercised no protection towards the guinea-pigs, and they all died within two days and a half, but the sera collected at the end of the experiment were, with one exception, definitely protective. The exception was that from cat 4, which had toxin-antitoxin only. Guinea-pigs protected with sera from cats 1, 2 and 5 did not die at all, and those which had serum from cat 3 lived many hours longer than the controls. It was therefore concluded that four of the cats had produced considerable quantities

of diphtheria antitoxin during the course of the experiment; the fact that they could at the end stand large doses of toxin (20 m.l.d.) on three successive days was almost sufficient proof of this, a single dose being lethal to average-sized control cats.

A microscopical study of the spleens of these cats showed no increase of mononuclear cells and none of the large basophilic cells at all; there was pyknosis of many of the lymphocytes in the follicles in all except cat 4, which was entirely normal. The bone marrow showed no change.

To summarize, then, four cats in whose sera high titres of diphtheria antitoxin were demonstrated after treatment with toxin, showed no changes in the spleen similar to those seen in acute infections.

Vaccines were prepared from cultures of two virulent strains of *Staphylococcus aureus* which had been shown to produce infections in cats and the characteristic changes in the spleen. Five cats were treated with daily doses of these vaccines for periods varying from ten to thirty-two days. Blood-serum was taken at the beginning of the experiment and found to contain no agglutinins. The vaccines were cultured before and after use and found sterile. White cell counts were made at intervals, and in each case a high leucocytosis (from a normal of 13,000–15,000 to 21,000 – 39,000) ensued. Agglutinins could only be demonstrated in low dilutions (1 in 5) of the final serum in two cats; in the other three no agglutinins were found. At autopsy the organs appeared normal, but microscopically there was marked hyperplasia of the bone marrow and a change in the spleen in all respects similar to that seen in acute pyogenic infections. (Fig. 7.) There were numerous large mononuclear cells

with basophil cytoplasm, myelocytes and polymorphonuclear leucocytes.

In summary, therefore, five cats treated with *Staphylococcus aureus* vaccines developed a high-grade leucocytosis and barely demonstrable anti-bodies. The spleens were not grossly enlarged or softened, but showed changes identical with those found in acute pyogenic infections of mild virulence.

## DISCUSSION.

A microscopical study has been made of large numbers of spleens from autopsies on persons dying of acute pyogenic infections and the application of micro-chemical tests, such as the oxydase reaction, suggests very strongly that the principal change is one of extra-medullary myelopoiesis; the large cells which have previously been described variously as plasma cells, endothelial cells, and the like are in reality myeloblasts, similar in function if not in origin, to those of the bone marrow.

An analysis of a number of such cases supports this thesis by showing a close agreement, on the whole, between the degree of leucocytosis achieved before death and the extent of the splenic change. There were, however, some cases which were apparently contradictory, and a discussion of these is essential. One was a man of forty-three who had cystitis and pyelonephritis for a month; his leucocyte count did not rise above 8,800, and yet he had quite an advanced acute splenic tumour. His general reaction was poor; the bone marrow was scanty and there were not many myelocytes in the sections. One would be inclined to explain the splenic change here as a last desperate but unsuccessful effort to produce leucocytosis. Another precisely similar case in a man of fifty-four may be

explained in like manner. Then there were two cases of extensive general peritonitis after appendicitis where the leucocyte counts were 5,000 and 9,000 respectively, and hyperplasia of the bone marrow and advanced splenic change were present. One may suggest that in these instances the destruction of leucocytes in the peritoneal exudate was so great as to exhaust the supply in the blood-stream.

The condition of so-called agranulocytic angina, in which there is extreme leucopenia in the presence of pyogenic infection, is an interesting one in this connection. In those cases that were found in the Johns Hopkins autopsy records there was, as a rule, a very loose splenic pulp with few cells. There were some myeloid cells present and a very few of the large basophilic mononuclear cells, which I regard as myeloblasts, but practically no polymorphonuclear leucocytes either in the pulp or in the sinuses; in these cases the bone marrow was also poor in cells. Here, then, is a disease in which, were there not some factor, probably toxic, which inhibits leucocytosis, one would certainly find an advanced acute splenic tumour.

There was also an interesting case of typhoid fever in a child of four years in whom there was a terminal infection with a pneumococcus lasting three weeks. During this time the leucocyte count rose from the low value obtaining in typhoid to 24,000/c.mm. The bone marrow was definitely hyperplastic, and the spleen showed quite a well-marked change in which the characteristics of typhoid infection were present, together with those of acute splenic tumour.

In cases of sub-acute rheumatism which died in an attack no changes were found in the spleen, and there was no leucocytosis.

Another point of importance arising from a study of these autopsies is that whenever there was an "acute splenic tumour" there was also hyperplasia of the bone marrow. The same was true in all my experimental animals.

With relation to the question of the association of immune body formation and the condition of acute splenic tumour, I have, in addition to my own experiments, had the opportunity of examining the spleens of rabbits and guinea-pigs which had been recently immunized against pneumococci and other organisms by other persons working at Johns Hopkins. These animals were given smaller doses of antigen than I used, and time was allowed for the formation of easily demonstrable anti-bodies. In these spleens there was no suggestion of any change. No record was made of the blood counts in these cases, but the fact that I found in my animals splenic changes with leucocytosis and without anti-body formation is very significant. It will be remembered that I also produced considerable amounts of diphtheria antitoxin in my cats without leucocytosis or splenic change, and diphtheria, unlike typhoid, is a disease where, in man and animals, leucocytosis and acute splenic tumour are found.

It now remains to decide the origin of these large myeloblastic cells in the spleen, and here one can speak with very little confidence. The same difficulty is experienced in attempting to account for the appearance of myeloid cells in the spleen and elsewhere in such conditions as osteosclerotic anæmia. Ehrlich's original view that the myeloid cells reached other organs from the bone marrow by way of the blood-stream is generally discredited, largely because they are not found in the blood. Jolly and Rossello,[25] in a study

of the development of the rat's spleen, found that primitive splenocytes gave rise later to cells with finely granular basophil protoplasm, and these to eosinophil and neutrophil myelocytes, mast cells, etc. They thought also that the lymph cells of Malpighian bodies were derived from primitive splenocytes. Megacaryocytes appeared later, and seemed to have a similar origin. The development of the splenic pulp ran parallel with that of the bone marrow, but there were fewer granular cells in the spleen; it appeared that myelopoiesis in the spleen was less important than in the bone marrow.

Whatever may be one's views on the origin of blood cells it is certain that myeloid cells are produced in the adult spleen when occasion demands.

## SUMMARY.

1. In acute pyogenic infections splenomegaly is due to an increase in the number of cells in the pulp, and in the Malpighian bodies in some cases.

2. The most striking cells which are present are large basophilic non-granular mononuclear cells which are identical with myeloblasts.

3. The degree of splenic change corresponds with the leucocytosis.

4. The identity of the infecting organism is of less importance *quâ* the spleen than the grade of leucocytosis it produces.

5. Pyrexia alone does not produce "acute splenic tumour."

6. The production of "acute splenic tumour" is not essential for, or directly related with, anti-body formation.

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# A CASE OF VON RECKLINGHAUSEN'S DISEASE (MULTIPLE NEUROFIBROMATA) WITH SPONTANEOUS FRACTURES.*

BY

L. P. ASHTON.

THE case to be described was one in which spontaneous fractures of the neck of each femur occurred, the skiagrams showing well-marked rarefaction in the ends of these bones.

The condition as originally described by von Recklinghausen was that of changes in the skin and cutaneous nerves alone; further research on the subject, however, has disclosed bone changes among the disturbances associated with the disease.

Although von Recklinghausen, in 1882, was the first to describe the pathology of the disease, it is interesting to note that one of our own countrymen, Robert W. Smith, after research in two cases, published an account of the condition in 1849. Von Recklinghausen, however, was the first to offer the now accepted theory of neuro-fibromatosis.

The disease is characterized by multiple painless nodules in the skin, irregularly distributed over the whole trunk and limbs, usually most abundant on the abdomen and back. The nodules are situated in the skin or subcutaneous tissues, and are not usually adherent to deeper structures. They may become

* This Essay was awarded a Martyn Memorial Pathological Scholarship.

pedunculated, but often remain deep enough to be invisible on the surface. They vary in size from a few millimetres to an inch or more in diameter; and may even develop to an enormous size when they become pedunculated, causing the condition of elephantiasis neuromatosa.

Microscopical examination reveals a fibrous nodule arising in a cutaneous nerve filament. It may be on the side or in the centre of a nerve, and in the latter case the nerve fibres will be seen spreading out and enclosing the tumour. This is said to originate from the connective tissue elements of the nerves, especially from the sheath of Schwann; tumours never arise in the olfactory or optic nerves, which are devoid of this sheath. The structure presents interlacing hyaline fibres, between which lie a few or many compressed tumour cells, the older tumours being almost completely fibrous. All the elements of the nerve filament or nerve trunk, except the ganglion cells and nerve fibres, participate in the tumour process. Nerve fibres in a state of degeneration can usually be demonstrated passing either over or through the tumour. Later in the disease the nerve trunks are similarly affected in any situation between the nerve root and the periphery. Motor or sensory phenomena follow damage to these nerves from pressure, especially if the tumour arises near the nerve root in the spinal canal or cranium.

Pigmentation is present in most cases in the form of freckles, blotches, or diffuse areas, often situated in relation to the underlying nodule.

*Bone changes* are said to occur in about 7 per cent. of the cases. There is some diversity of opinion as to the exact nature of the change, but the weight of evidence goes to show that the lesion is similar to

that of osteomalacia. There can be little doubt that the condition is not in any way connected with osteitis fibrosa, for as Gould[1] demonstrated, there was no deposition of fibrous tissue in the medullary cavity of a femur examined by him, a feature always present in osteitis fibrosa.

In research carried out on microscopical sections of bones in von Recklinghausen's disease Gould showed that, in a decalcified bone, there was absence of abnormality in general structure and in the relative proportions of bone substance and marrow. The Haversian spaces were quite normal and were nowhere dilated, the condition found in very advanced osteomalacia.

In an undecalcified section the main feature was the large amount of bone devoid of lime salts, that is in the condition of osteoid tissue. The centrally-placed bone could be seen surrounded by the osteoid tissue, which also lined the Haversian canals and covered the bony trabeculae. The osteoid present was considerably in excess of the true bone. These changes are similar to those seen in early osteomalacia, and, consequently, suggest the connection between that condition and the disease under consideration. Both conditions are possibly brought about by alteration of internal secretions, the manifestations of both being exaggerated by pregnancy, becoming less again after delivery.

Subperiosteal nodules are frequently present, and on section there have been found to be swellings covered by very cellular periosteum and containing large irregular bone corpuscles. Brooks and Lehman[2] state that subperiosteal nerve involvement leads to the reaction of destruction and regeneration of bone; a thin shell of bone is deposited by the periosteum

which may be palpated on the bone. In consequence of the destructive process cysts are formed under the periosteum; these may be small (as in the left tibia, Fig. 5, A), or may reach the size of the thickness of the bone. These cysts usually become filled with dense fibrous tissue. The hyperæmia brought about by the reaction throughout the bone may cause thickening and lengthening of the bone affected.

The disease may be hereditary or congenital. Osler states that in one family three generations were affected, and in another the mother and several children. On the other hand, the bone changes and pigmentation possibly suggest some endocrine disturbance as the underlying cause. No definite conclusion, however, has yet been reached.

The clinical record of the case is as follows:—

Female, aged 47. Domestic servant. She gave a history of erythema nodosum in 1924 and broncho-pneumonia with pleural effusion in 1927. In the family history no traces of von Recklinghausen's disease can be found.

*Present history.*—The patient was taken for the first time with sudden sharp pain in the right hip-joint, causing her to fall down. After admission to the Bristol General Hospital an X-ray examination revealed a transverse fracture to the neck of the left femur. Eleven months later, after the patient had been walking round the ward with the aid of crutches and Thomas's walking calliper, another skiagram was taken, which showed a fracture of the neck of the right femur, the lesion having occurred without previous signs or symptoms.

*State on Examination.*—The patient [illegible] thin and pale with a dry, rough skin. A number of small [illegible] nodules up to 1 c.m. in diameter were present on the trunk, some rounded, others pedunculated. Blotchy pigmentation was present on the abdomen and chest, and in the form of freckles on the legs and arms.

The flexures of the limbs were the sites of firm, nodular enlargements, which were deep to the tendons but not fixed to the bone, and did not appear in the skiagrams. These swellings were seen at the elbows, wrists, knees, and groins,

# PLATE XIII.

FIG. 1.
Miss E. G. December, 1929.
X-ray to show changes in ribs and right humerus.

FIG. 2.
Miss E. G. December, 1929.
X-ray to show change in shaft of left femur.

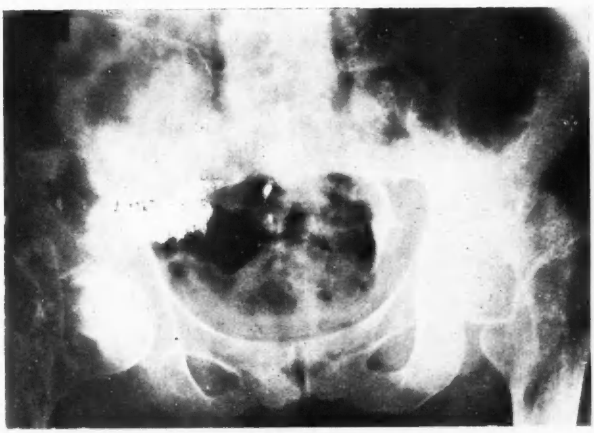

FIG. 3.
Miss E. G. December, 1929.
Showing fracture of the necks of both femora.

# PLATE XIV.

FIG. 4.
Miss E. G. December, 1929.
Advanced rarefaction near left knee-joint.

A. FIG. 5. B.
Miss E. G. December, 1929.
Subperiosteal cystic change in left tibia.

and the average size was equivalent to that of a walnut. Growth was very slow except in the case of the one in the right groin, which attained the size of a tennis ball in a few weeks; this tumour was smooth, round and fixed, and the femoral artery could be seen pulsating superficially to it. None of these swellings gave rise to pain, and there was no history of previous neuralgia or headache. After a year no further nodules appeared, and the ones already present decreased considerably in size. Subperiosteal nodules could be palpated along the posterior border of each ulna and down the antero-internal surface of each tibia.

A nodule was excised from the anterior fold of the left axilla and sections were cut. Microscopically the section consisted of fibrous tissue with only a few scattered tumour cells between the fibres, indicating that the tumour was one of somewhat slow growth.

*Bone Changes.*—The entire skeleton was X-rayed twice with an interval of nine months between. The change in the bone appeared to be progressing slowly in the tibia and left femur, and to be stationary in the remainder of the skeleton.

The skiagram taken in December, 1929, showed fractures in the neck of each femur, with very advanced absorption of bone in the region of the fracture on the left side, the neck being almost completely absorbed on that side. (Fig. 2.)

Three types of rarefaction could be demonstrated in the skiagrams:—

1. A diffuse type was seen in the pubes, lumbar vertebræ and thorax, probably due to disuse. (Fig. 3.)

2. A patchy type was well marked in the left femur and tibia. This change was seen mostly in the neighbourhood of joints, those affected to the greatest extent being the knee and ankle, but similar changes were also present near the elbow, wrist and hand joints.

This discrete patchy type appeared to be due to the subperiosteal nodules and cysts which have been demonstrated in the bone. These appeared in the skiagram, and could be palpated in the respective bones, *i.e.* tibia and ulna, one situated on the tibial crest being most readily demonstrated.

3. A somewhat grosser cystic type of rarefaction with the diffuse type superimposed was present in the proximal two-thirds of each femur and humerus, also in the patella and condyles of the left femur. (Figs. 1 and 3.) It was

in these areas that the osteomalacic changes were most marked, whereas in the left tibia the subperiosteal nodules predominated.

Types 2 and 3 were clearly the result, not of simple disuse, but of definite neurotrophic disturbance of a different character.

*The Joints.*—There was much thickening of peri-articular tissue in the ring and little finger of each hand, causing complete immobility of these fingers. The other fingers were affected, but to a lesser degree. The swellings in the flexures of the other joints described above were the cause of limited movement, the joints themselves after careful examination appearing to be quite normal.

The only nerve change that could be demonstrated was the complete loss of pain, temperature and touch sense in the index and middle fingers of the left hand. This had been present for many years. This lack of nerve signs went to show that there was little or no involvement of nerve roots in the spinal canal and cranium.

In reference to the calcium deficiency of the bone, the blood calcium was estimated and found to be slightly reduced—0·0092 per cent., the normal being 0·01 per cent. This was not enough to account for the excessive loss of calcium in the bone.

To exclude specific changes in the hip-joints the Wassermann reaction was carried out and found to be negative.

## SUMMARY.

A case of von Recklinghausen's disease (multiple neurofibromata) is described in which bone changes were noted. These included spontaneous fracture of the necks of both femora. The nature of these bone changes is discussed.

Thanks are due to Dr. Carey Coombs for permission to use the notes and to Dr. Macdonald Critchley for his comments on the case.

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# THE ORIGIN AND SIGNIFICANCE OF TUBERCULOSIS OF THE TRACHEO-BRONCHIAL LYMPH NODES OF THE LUNG.*

BY

L. R. JORDAN.

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## INTRODUCTION.

THE frequency of latent tuberculosis has been recognized since the latter part of the seventeenth century, but the true significance of these latent lesions in relation to other tuberculous conditions has not received the attention they merit. Recently, however, Continental and American workers have thrown some light on this important subject. In particular, E. L. Opie,[1] of Pennsylvania, points out the following two conflicting factors which must be considered when dealing with "latent tuberculosis."

1. The increased resistance to the disease from a somewhat ineffective immunization.

2. The danger that latent infection may cause manifest and perhaps fatal disease.

The significance of these factors with regard to latent disease will be discussed in the following remarks. The notes from 33 cases of tuberculosis examined post-mortem at the Bristol Royal Infirmary during the last two years, with either tracheo-bronchial or

* Awarded a Martyn Memorial Pathological Prize.

mesenteric infection associated with acute miliary tuberculosis, were used in preparation of this paper.

*Latent Tuberculosis.*—This may be defined as a tuberculous infection unaccompanied by significant symptoms evident to the patient or by physical signs discoverable by the physician.

The important question involved is, at what period of life does latent tuberculosis exist? In the early years of childhood tuberculous infection nearly always proceeds to tuberculous disease, which is usually fatal, ending as acute miliary or acute pulmonary tuberculosis. Where the primary lesion is in the abdomen and thorax, for a short time, at least, there exists a "latent" period, during which no physical signs are discoverable at the routine clinical examination. Of the 26 cases of tracheo-bronchial and mesenteric tuberculosis at the Bristol Royal Infirmary only 3 cases at post-mortem revealed death due to causes other than tuberculosis, and the youngest was 7 years of age. MacNeil [2] reports a larger number of cases of latent tuberculosis, 18 in all: 1 case occurred under 2 years, 6 between 2 to 5 years, the remainder over 5 years, and he concludes that latent tuberculosis can scarcely be said to occur in infancy. Unfortunately MacNeil does not define his use of the word "latent," but he obviously means dormant or inactive tuberculosis. The definition given above may include active as well as dormant disease without physical signs, and the former, as will be seen, does exist during childhood, but is rarely recognized during life.

*First Infection with Tuberculosis.*—Tuberculosis in infancy and early childhood, which resembles that of

an animal inoculated with tubercle bacilli, forms a lesion at the site of infection and quickly affects the nearest lymph nodes.

How far is this true in the human being? The commonest sites for lymph-node infection are, firstly, the tracheo-bronchial glands in the hilum of the lung, and, secondly, the mesenteric glands. In the latter case the lesion at the site of the infection occurs in the intestine or, as shown recently, may not form a visible intestinal lesion.

In the former case much controversy has taken place as to the site of primary infection. Some maintain that the lesion in the tracheo-bronchial nodes is primary. The majority of the evidence now seems to point to the lesion being secondary to a primary lesion in the periphery of the lung drained by the lymph nodes. When diligently looked for, a primary peripheral focus in the lung tissue has been shown to be present in the majority of cases.

Evidence in favour of this also supports the air-borne infection theory of tuberculosis, since the primary focus at the periphery of the lung occurs usually in a small bronchiole.

*Modes of Infection in the case of Tracheo-bronchial Tuberculosis.* — For the present purpose only two paths of infection need be considered, respiratory and alimentary. Both are equally probable in the child, the first from association with adult phthisical cases, the second by taking infected milk in its diet.

The belief that *infection through the respiratory tract* may occur is supported by the following evidence :—

1. In anthracosis and allied diseases coal and other dusts can be inhaled deeply into the lungs.

There is no reason why bacilli should not be inhaled in droplets or dust particles and give rise to lesions in the lung.

2. Guinea-pigs exposed to dust or spray laden with tubercle bacilli were found on necropsy, some time later, to show lesions in the most distant bronchioles and alveoli, and tubercle bacilli were recovered from these parts.

3. Ghon,[3] and more recently MacCallum[3] demonstrated in every case of tuberculosis of the lungs in children the presence of an old primary lesion in the extreme periphery of the lung followed by lymphatic transportation to the bronchial nodes. Kuss[4] who also found the nodule in almost every case, and Opie who confirmed the results, regarded "the consistence and nature of the nodules as evidence of considerable age and typical of lesions sustained during childhood." Canti[5] in his own cases states that the changes in the glands never appeared older than those in the lung focus. He also regards it as proved "that tuberculous tracheo-bronchial glands are not secondary to a focus anywhere else in the body."

Recent work by Miller on the pulmonary lymph flow makes it difficult to accept the view that a retrograde infection from the hilum to lung tissue can occur.[6] Krause, however, has shown experimentally that organisms may pass through the lung tissue, leaving the latter unaffected, and produce the primary lesion in the lymph nodes.[6] This is probably very rare in the human being, but it may account for rare cases of lymph-node infection which do not reveal a primary lesion on careful examination.

Of the 20 cases of tracheo-bronchial tuberculosis seen at routine post-mortem examinations 5 showed definite primary foci in the periphery of the lung. In the remaining 15 cases the lesions were most probably present, but overlooked for the following reasons :—

1. No special search was being made.

2. The nodules can be very minute, and without careful dissection not easily found. Krestin[6] remarks that X-ray films of the excised inflated lungs are a great aid to their detection.

3. In adults showing hilum infection the primary lesions were most probably healed and represented by a small scar.

4. The primary lesion may be masked by co-existent miliary tuberculosis, or by tuberculous broncho-pneumonia and secondary septic conditions which are present in a majority of cases.

The 5 cases in which the primary foci in the lung tissue were well marked and easily discovered were all in children under 7 years, and the lungs in these cases did not show any other gross obscuring lesions. Two specimens were kept showing tracheo-bronchial tuberculosis of the lymph nodes and primary foci in the lung tissue.

**Case 1.**—Male, aged 7, whose left lung showed the following lesions. (Fig. 1.)

At the apex of the upper lobe of the left lung there was a patch of quiescent tuberculosis ; this was the primary focus. It consisted of two caseous nodules surrounded by a definite fibrous thickening, measuring about 2 cm. by 1 cm. A second smaller caseous nodule was visible under the pleural surface some distance away. At the hilum is one enlarged caseous " sentinel " gland at the upper part, which corresponds to the gland draining the infected area. There are some other enlarged hyperæmic glands in the hilum with no sign of

caseation, they are probably early tuberculous. The primary lesion appears to be much older than the glandular infection, as judged by the degree of fibrosis and caseation.

This case did not show any military tuberculosis. Death was due to another cause, acute myocarditis and subacute endocarditis.

**Case 2.**—Female, aged 4 months. (Fig. 2.) The lesion progressed rapidly and ended in tuberculous meningitis with acute miliary tuberculosis of the spleen and kidney.

The right lung, lower lobe, showed a small caseous area with small cavities. A caseous gland at the hilum, corresponding to the area drained by lymphatics, was present, and showed an area of recent spread into the lung. There was practically no fibrosis, showing that the lesion had progressed rapidly, entered the blood-stream and scattered as miliary tuberculosis throughout the body.

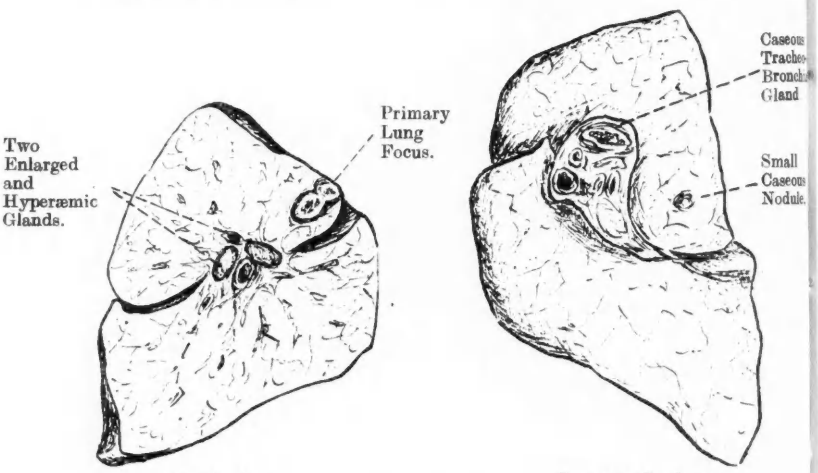


FIG. 1.—Lung from a male child, aged 7 years.

The cut surface shows a large primary focus in the upper lobe; it consists of two caseous nodules surrounded by a definite fibrous thickening. Measures 2 cm. by 1 cm.

The hilum shows an encapsulated caseous tracheo-bronchial gland and several enlarged and hyperæmic glands cut through. These show no caseation, but one probably tuberculous, being recently infected by lymphatic or direct spread from the other gland.

A small caseous nodule is also seen on the pleural surface of the upper lobe.

Both the primary focus and the tracheo-bronchial gland show a degree of fibrosis not seen in those rapidly growing lesions ending at a much earlier age in acute miliary tuberculosis.

Death in this case due to acute myocarditis and subacute endocarditis.

*The alimentary route* in infection of tracheo-bronchial glands has not so much evidence in favour of it as the respiratory. Nevertheless, lungs which do not show a primary lung tissue lesion in tracheo-bronchial tuberculosis may possibly be infected by means of the lymphatics or blood-stream from the alimentary canal. This would seem to account for the bilateral infection of tracheo-bronchial lymph nodes, which does occur without any easily-found primary focus.

Usually the majority of lesions in tracheo-bronchial tuberculosis occur on the right side. In this series 8 cases out of 14 cases of tuberculosis were right-sided, 4 being left-sided and 2 occurring on *both* sides. (Six of the cases had to be excluded, as the notes did not state definitely on which side the lesions occurred.) These figures agree with Wollestein's, who found 74 per cent. lesions on the right side.[8]

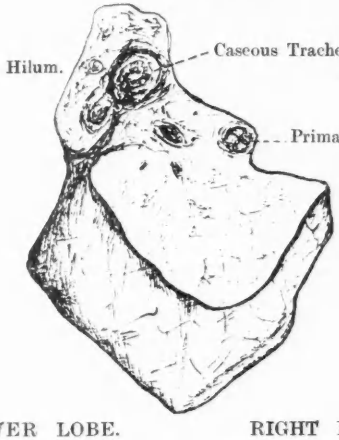


FIG. 2.—Lung from a female child, aged 4 months.

A portion of the right lower lobe showing the position of the primary focus in the lung substance, and the secondary involvement of the tracheo-bronchial gland at the hilum of the lung.

Neither lesion shows much fibrous thickening around it, indicating a rapid and fatal spread. Death in this case due to tuberculous meningitis and acute miliary tuberculosis.

Even in the case of those lungs which show a primary focus in the lung tissue, the possibility of the original bacilli reaching the lungs by the circulation, and there forming a tubercle, with subsequent lymph-borne infection of tracheo-bronchial glands, cannot be excluded in every case.

Von Behring[3] points out that in very young infants the ferment-secreting glands of the digestive tract are little developed and the epithelial lining not yet a serious obstacle to the passage unchanged of any foreign protein. A rapid general spread of such bacteria throughout the body, lodging in the lymphoid tissue everywhere, is usual without any lesion in the intestinal mucosa.

Experimentally, pigment given to animals by mouth finds its way from the alimentary canal and collects in the lungs and bronchial glands, showing that the latter have some peculiar filtering effect. Further studies, however, indicate that tuberculosis is conveyed to susceptible animals with much more difficulty by way of the gastro-intestinal tract than by way of the lungs.[1]

*Formation and Growth of Tracheo-bronchial Tuberculosis.*—The extent of latent tuberculosis of the tracheo-bronchial glands in adults has been investigated by Krestin.[6] He notes that even in very gross lesions the process is invariably limited to the gland capsule, and in no case invaded the surrounding connective tissue. In those adult cases seen at post-mortem in the Bristol Royal Infirmary a definite fibrous capsule was generally present around the tuberculous gland. In children and adults when the glandular infection has proceeded to fatal disease the fibrous capsule was either poorly formed (indicating rapid growth),

or recent spread through the neighbouring tissue was observed.

The growth of tracheo-bronchial tuberculous lymph nodes is rapid and destructive, especially in the young child. Except when latent tracheo-bronchial tuberculosis is present the lymph nodes at the hilum are not conspicuously affected in the adult. Apparently there has been time for resistance to develop to such a degree that the destruction of tissue is held in check. The infant does not develop this resistance until it has reached several years of age, and it increases with the age of the child.

Tracheo-bronchial lesions after the early years tend more and more to heal and become latent. The majority of cases before 2 years of age, however, end rapidly in acute miliary or acute broncho-pneumonic tuberculosis.

Those cases which in later years of life become the "latent" lesions may or may not be the cause of more deadly disease in the adult. In the cases studied (9 cases of acute miliary tuberculosis between the ages 12–25 years) 6 cases showed tracheo-bronchial and 1 case mesenteric tuberculosis, and the remaining 2 cases were secondary to chronic phthisis. The remaining cases of tracheo-bronchial tuberculosis either end in tuberculous broncho-pneumonia (3 cases) or remain latent.

The earliest case in the series of tracheo-bronchial tuberculosis was a child of four months, probably the earliest recorded. The only other case under one year was a child aged 10 months, who showed tracheo-bronchial tuberculosis with miliary tubercles in the lung, pleura, liver and spleen. There was no meningitis in this case. Krause,[7] in experiments on animals, has recently shown that tracheo-bronchial gland

infection can take place in non-immune animals in from seven to forty days. In this case the presence of tubercle bacilli in the glands was demonstrated by injecting them into other guinea-pigs. In the child of 4 months infection has obviously occurred soon after birth, but in the majority of children in this series death occurred during the second year of life. Opie,[1] working on much larger figures, says that the first year of life shows the greatest mortality, followed by a gradual decline to the fifth year and over. He comes to the conclusion that tuberculous infection in childhood increases resistance to the disease, but is at the same time a source of danger.

*Acute Miliary Tuberculosis.*—As we have seen, the most likely result of tracheo-bronchial tuberculosis is acute miliary tuberculosis. It occurs as a fatal termination to those cases of rapid infection during childhood, or to previously latent disease at almost any age. In this series 75 per cent. of cases of acute miliary tuberculosis between birth and 5 years and 59 per cent. of these between 12–40 years of age showed tracheo-bronchial infection. According to the figures it is nearly six times as common during childhood (1–5 years) as in the adult (12–40 years), and a considerable number of cases are associated with tuberculous meningitis.

Of 29 cases at all ages in the series, 60 per cent. showed tuberculous meningitis, 45–57 per cent. miliary tubercles in the pleura or lung, 63 per cent. in the spleen, 57 per cent. in the liver and kidneys, and 25 per cent. in the peritoneum.

Tuberculous meningitis is thus the commonest form of death in the acute tuberculous diseases. Miliary tubercles of pleura and lung were present in

a large number of cases, four of which showed involvement of the lung only. In one case the pleura alone was involved. Of the abdominal organs the spleen was the most and the liver and kidneys less frequently involved. The lesions in the liver were chiefly subcapsular, miliary tubercles rarely being found in the liver substance. The peritoneum was only involved in a comparatively few cases. Miliary tuberculosis of the lung alone was not seen ; the cases, 16 in number, were all associated with miliary tubercles of the other organs, and 10 of these cases showed meningitis.

Of the 17 cases showing tuberculous meningitis all were associated with miliary tuberculosis of some other organ or organs.

In 3 cases of tuberculous meningitis no primary lesion was discovered at the routine post-mortem examination. These, the only cases of acute miliary tuberculosis in which this occurred, were, curiously enough, all females.

On the other hand, it may lend support to the theory, held by some, that this disease is sometimes primary in a small number of cases which fail to reveal primary lesions even on the most careful investigation.

The following table gives some idea of the distribution of such primary lesions as was found in the series :—

| Age. | Bristol Figures. | | | MacNeil's. | | |
|---|---|---|---|---|---|---|
| | Pulmonary. | Abdominal. | Cervical. | Pulmonary. | Abdominal. | Cervical. |
| Birth—2 years.. | 1 | 1 | 0 | 13 | 10 | 1 |
| 2—5 years .. | 4 | 1 | 0 | 9 | 4 | 0 |
| 5—12 years .. | 1 | 0 | 0 | 11 | 2 | 1 |
| Total .. .. | 6 | 2 | 0 | 33 | 16 | 2 |

Over 12 years of age the commonest period in the series of meningitis with tracheo-bronchial tuberculosis was from 15 to 25 years. Although from a much smaller number of cases, it is obvious from the above table that the majority of "primary" lesions occur in the chest (*i.e.*, tracheo-bronchial) from 2–5 years, showing a rise after the first two years, instead of a fall as MacNeil's figures show.

Comparing the figures of the abdominal cases, it will be seen that, apart from the difference in numbers, they correspond as far as age incidence is concerned.

Though these small figures count for little, in this case they are probably borne out by larger ones, and the results may be put down to a difference in locality from which the cases were drawn.

Apart from the above-mentioned differences, there is ample evidence to support the general statement "that nearly all cases of tuberculous meningitis are derived from a glandular or visceral focus in the thorax or abdomen, a clear majority being thoracic."

It is uncommon for tuberculous meningitis to develop from glandular disease of neck and throat. No case was found in the series. The fact that all the cases of tuberculous meningitis were associated with the miliary tubercles in other organs indicates a blood-borne infection in every case. The possibility of a lymphatic or direct spread causing the meningitis seems very remote, and does not explain the cases in which no primary focus was discovered.

*Recognition of Tracheo-bronchial Tuberculosis during Life.*—This at present is a difficult matter. In none of the cases in the series was the presence of tracheo-bronchial tuberculosis recognized clinically, although

the majority ended fatally as acute generalized tuberculosis when it was too late for any interference. Opie[1] and others, by the use of the von Pirquet reaction and X-ray films of the chest, claim to have discovered a large number of cases of tracheo-bronchial tuberculosis during life. It has been found by this means that this disease is seven times more common in children exposed to massive infection from active phthisical cases in the family. Conversely, the discovery at post-mortem of tracheo-bronchial tuberculosis in children ending fatally may be a clue to the presence of active phthisis in one of the adults of the family, hitherto undiscovered. MacNeil[2] points out that a positive tuberculin test with or without positive skiagrams in children in early years is of grave significance, as the disease is rarely "latent" at this age, and active tuberculosis, as we have seen, is generally fatal.

## CONCLUSIONS.

1. The majority of evidence at present points to tuberculous infection of the tracheo-bronchial glands being secondary to a primary air-borne infection in the lung tissue.

2. Tuberculosis, especially of the tracheo-bronchial glands in children under 5 years, is not dormant, but in the majority of cases ends in fatal disease.

3. A considerable proportion of acute miliary tuberculosis, especially with tuberculous meningitis, in adults has its origin in tracheo-bronchial tuberculosis.

4. All the cases of tuberculous meningitis were blood-borne, and no explanation is offered for the absence of visible primary foci in these cases.

5. Tuberculous infection in childhood increases resistance to the disease, but at the same time is a source of danger.

I should like to thank Dr. Fraser for permission to use the post-mortem notes and pathological material, and for the encouragement he has given me in the preparation of this paper.

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[8] MacCrae, T., Osler's *Principles and Practice of Medicine*, 1927, p. 178.

# Reviews of Books

**On Faith and Science in Surgery.** By Sir John Bland-Sutton, Bart. Pp. xii., 109. 40 illustrations. London: William Heinemann Ltd. 1930. Price 7s. 6d.—This small volume consists of ten addresses delivered between 1925 and 1930 and put together under the rather misleading title above quoted. Curiosities of Science distantly related to Surgery would be perhaps a more accurate description of its contents. When a surgeon has become notorious as an interesting and witty speaker, he must find it difficult to choose fresh subjects for his addresses and to name them with attractive titles. Bland-Sutton more than any living man has inherited John Hunter's keen and insatiable curiosity about all the inexplicable phenomena of animal life, and therefore he takes some curious phase of normal or abnormal biology as his theme. The address on ligatures refers to the sewing of tailor birds and to the use of ants' mandibles as skin clips. Two addresses on the faith in drugs and physic are illuminated by references to the ancient practice of physic and to the natural concretions of animals. These latter have always had great vogue as healing drugs. The chapter on twins and monsters and that on the psychology of animals swallowed alive are full of absorbing interest. We are constantly reminded throughout the book of the marvellous versatility of the author. To begin with he is a zoologist whose resting thoughts always seem to hark back to the denizens of the deep sea or the wonders of the Zoo. Then he is an inquiring anatomist who has never ceased to ask questions and to find answers about such problems as those presented by hydrocephalus. He has been a pioneer in surgery; he tells the tale of how gall-bladders first began to be taken out; and a gynæcologist who unravelled the mystery of tubal moles and did so much for the perfecting of hysterectomy. He has a great fondness for versification and these literary efforts have neither rhyme nor rhythm: also a wonderful knowledge of the Scriptures, which he quotes and refers to on all occasions and often in a manner quite at variance with orthodox interpretation.

**A Short History of the Army Medical Corps.** By COLONEL F. SMITH, C.B., C.M.G., D.S.O., R.A.M.C. Pp. 111. Illustrated. Aldershot: Gale and Polden. Price 2s. 6d.—This little volume, we are told, is written for young soldiers of the Corps who have to pass examinations in the subject. For the general reader the chief interest in the book is the fascinating account of many of the chief deeds of valour by officers and men from the Crimea down to the present day. This forms what is perhaps the most astonishing chronicle of heroic actions by men of a non-combatant corps ever put forth. Though these graphic reports take up the greater part of the book, they are only a fraction of the glorious deeds by men of the corps for which twenty-eight V.C.'s and thousands of other honours were awarded, and they form one of the best answers to the recent depreciating of war books. The author traces the gradual evolution of the Corps from the days of the old chaotic regimental system and the Crimean breakdown to the creation of the present body in 1898 near the end of the long series of Egyptian expeditions. The Corps were barely formed when we were involved in the great South African War where 22,000 men died and 76,000 were invalided. In the last Great War the Corps dealt with near nine millions of sick and wounded, and healed and sent back to the firing-line in France alone over one and a half million of wounded men, while nearly 7,000 of its officers and men gave their lives. In a subsequent edition the first chapters on the original formation of the Corps might with advantage be revised and condensed.

**Diagnosis and Treatment of Heart Disease.** By E. M. BROCKBANK, M.D., F.R.C.P. Sixth Edition. Pp. xvi., 240. Illustrated. London: H. K. Lewis & Co. Ltd. 1930. Price 7s. 6d.—The sixth edition of Dr. Brockbank's book on the *Diagnosis and Treatment of Heart Disease* is somewhat larger than the previous edition, but is still easy to read. The book should be of great use to students before sitting for their examinations. Dr. Brockbank's theory of the causation of the crescendo murmur of mitral stenosis is not accepted by cardiologists, but we notice that this fact is mentioned in the text and should therefore not be a danger to the reader. The author has taken the trouble to explain the meaning of the physical signs in simple language; a most useful thing for students who are rather apt to take things for granted and not to ask the reason why. It is a book which should be on the shelves of all the University libraries.

**The Action of Muscles.** By SIR COLIN MACKENZIE, M.D., F.R.C.S., F.R.S. Second Edition. Pp. xvi., 288. Illustrated. London: H. K. Lewis & Co. Ltd. Price 12s. 6d.—It is doubtful if this book will ever be widely read, which is a pity. It is full of interesting items of information which provoke one to think and to reconsider theories and practices which have been taken too much for granted. The excellent matter which it contains is very badly presented to the reader. Items of anatomy, pathology, physiology, comparative anatomy and treatment follow one another without any method. A drastic rearrangement of the whole volume would be well worth while. It is well printed, illustrated and indexed and will repay a patient study.

**General Practice.** By ERNEST WARD, M.D., F.R.C.S. Pp. viii., 108. London: John Bale, Sons and Danielsson, Ltd. 1930. Price 3s. 6d.—It may be an oversight, but the reviewer has failed to find in this book any statement to the effect that general practice is doomed. This alone is enough to show that the author is no ordinary man. The book is a kind of sequel to *Medical Adventure*, reviewed in these columns not long ago, and is as delightful. It is brief but full of wisdom. Take, for example, this paragraph: "Let me say again that there are three kinds of treatment. First, *physical* treatment; by rest in bed, warmth, local applications, and by drugs. Second, *mental* treatment; by no means confined to Christian Scientists. . . . Third, *social* treatment; it is necessary to create a suitable atmosphere around the patient." Happy is the young practitioner who is taught these lessons by example. If, however, this is not available, he may well be grateful to Dr. Ward for his precepts. Discerning relatives should certainly give him a copy of the book on his next birthday.

**Clinical Examination of the Nervous System.** By G. H. MONRAD-KROHN, M.D., F.R.C.P. Fifth Edition. Pp. xvi., 222. Illustrated. London: H. K. Lewis & Co. Ltd. 1930. Price 7s. 6d.—This book has been reviewed several times previously in our columns, when it was described as a most valuable guide for the examination of the nervous system. That it has now reached its fifth edition in ten years shows that its value has been appreciated and that it filled a very definite need. The present edition has again been revised and short descriptions of ventriculography and encephalography have been added.

**Visceroptosis and Allied Abdominal Conditions.** By H. BEDINGFIELD, M.D., M.R.C.P. Pp. 176. London: Oxford University Press. 1930. Price 10s. 6d.—This monograph deals with a difficult subject of the highest clinical importance, in an entirely admirable manner. It deserves the careful consideration of every general practitioner and no operating surgeon can read it without qualms, when he looks back on some of the failures of his surgical career. The book opens with a dramatic and wonderfully vivid clinical picture of the chronic abdominal invalid. The author passes in review Glénard's theories of visceroptosis and the theories which have held the field subsequent to the introduction of X-rays. These theories, in the main mechanical, are subjected to a searching and destructive criticism. The author shows that considerable range of movement and variation in position of the hollow viscera are consistent with perfect health, and that such variation is due to physiological or physical causes. In the abdominal invalid the defect is due to malfunctioning of the neuro-muscular mechanism, behind which there lies a strong constitutional factor. The autointoxication theory associated with constipation as presented by Lane is attacked and controverted. These unfortunate abdominal invalids are over and over again the victims of injudicious surgery: not infrequently a single patient has a history of multiple laparotomies to his credit and the surgeon's shame. The views of the author on surgical intervention are summarized in the following passage: "Nothing is more disastrous than surgical intervention in the chronic intestinal invalid. As a method of treatment it is useless; as a method of diagnosis it is criminal." The chapter on treatment is careful and most helpful. The book contains a very complete bibliography of the subject.

**Diathermy, Medical and Surgical, in Oto-Laryngology.** By DAN MCKENZIE, M.D., F.R.C.S.E. Pp. xiv., 184. 23 illustrations. London: Kegan Paul, Trench & Trubner. 1930. Price 10s. 6d.—This exceedingly interesting and valuable contribution to the therapeutic application of diathermy is the work of one who has long been known as an enthusiast. Nevertheless, it is essentially practical. For example, of diathermy dissection of the tonsil for malignant disease the author observes that this "is not as easy as it sounds,"—the utterance of experience so invaluable to the novice. Detailed consideration is given to the various problems that present themselves, and the views put forward are those always of the critic rather than of the advocate.

**The Physiological Principles of Hydrology.** By R. G. GORDON, M.D., D.Sc., F.R.C.P., and F. G. THOMSON, M.D., F.R.C.P. Pp. 129. London: J. Cape Ltd. 1930. Price 5s. —Books on hydrology are as a rule rather dull and uninteresting to the general practitioner. The present volume, however, instead of giving details of the chemical constitution of the waters and a list of the Spas which are suited to various diseases, has set forth first the physiology of the skin, circulation, nervous system and metabolism in relation to hydrology, and after discussing the internal and external use of the waters, deals finally with their application to a variety of diseases. We are glad to see that emphasis is laid rather upon the physical than the chemical properties of the waters, and that a warning note is sounded in reference to the treatment of all forms of myocardial disease by Nauheim baths. The historical sketch of the use of hydrology is full of most interesting and amusing matter.

**Shorter Convalescence.** By LIEUT.-COL. J. K. MCCONNEL, D.S.O., M.C. Pp. xi., 130. London: William Heinemann Ltd. 1930. Price 5s.—This little book will be of interest alike to the general practitioner and the specialist, for both classes have at some time under their care cases recovering from acute illness and also those to whom Goldthwait refers as a discredit to the medical profession, *i.e.* the "chronic cases." Col. McConnel's suggestions cannot fail to help to reduce the period of invalidity of the former and prevent many of them from being added to the classes of the chronic. We must all be familiar with cases in whom relief of the acute abdominal condition, for which they were operated on, was associated with the development of chronic backache or flat-foot from lack of attention to postural considerations during their convalescence. The introduction of the simple exercises advocated by Col. McConnel, as a routine for all recumbent patients who have passed the acute stage, would prevent such disasters. The author has made an intensive study of his subject and gives a valuable bibliography, while within the small compass of his book he manages to provide a simple and interesting summary of the most modern work in connection with the maintenance of posture and the re-education of correct posture in subjects who have either failed ever to attain it, or have lost it through illness or strain. The evolution of upright posture in man, its physiology as a series of conditioned reflexes, in which muscles that are

antagonists for movement contract synergically, and the influence on the circulation of muscle action and diaphragmatic respiration, are all dealt with briefly but clearly. In his introduction, the author agrees that certain acute conditions "may preclude exercises of even the mildest description," but points out that even soon after a laparotomy, "co-ordinated tightening of the abdominal wall can be made without any pain, especially if this takes place automatically." One must agree with Sir Robert Jones, who in a foreword says "this book deserves a wide circulation."

**The Elements of Medical High Frequency and Diathermy.** By W. C. DOUGLASS, M.R.C.S., D.M.R.E. Pp. viii., 136. 67 illustrations. London: H. K. Lewis & Co. Ltd. 1930. Price 6s.—It is a bold undertaking to explain in a hundred pages the theory and method of producing high frequency and diathermy currents: the more so when the reader is initially supposed to have attained a knowledge of electricity that would hardly take him through the preliminary M.B. examination. While the elementary theory of dynamos and of induced and oscillating currents is clearly expounded, it seems very doubtful whether the intended reader will attain a sound knowledge of high frequency and diathermy from an account necessarily very condensed. The descriptions of diathermy apparatus are little more than the short accounts provided by the various makers for catalogue purposes and the author utters the warning that the practical application of medical electricity must be sought in more extensive works.

**Synopsis of Surgery.** By E. W. HEY GROVES, M.S., M.D., B.Sc., F.R.C.S. Ninth Edition. Pp. viii., 676. Illustrated. Bristol: J. Wright & Sons Ltd. 1930. Price 17s. 6d.—When a book has hastened to a ninth edition, the task of the reviewer is a light one. His only duty is to point out wherein the new edition is an improvement on its forerunners. The sections on surgical shock, spinal anæsthesia, glossitis, tumours of the bladder and testis, and infections of the kidney have been largely rewritten. It is not surprising to find that Professor Hey Groves' own new methods of treating fractures of the neck of the femur are noticed. New articles appear on the injection treatment of varicose veins, tuberculous bladder (we remember calling attention, in reviewing a former edition, to the lack of this) and the Winnett Orr treatment of septic conditions of bone.

**The Mycoses of the Spleen.** By ALEXANDER GEORGE GIBSON, M.D., F.R.C.P. Pp. xii., 169. Illustrated. London: Kegan Paul, Trench & Trubner. 1930. Price 12s. 6d.—In 1912 the author of this book demonstrated mycelial structures in the spleen from a case of Banti's disease. The mycelium was found in the Gandy-Gamna nodules—small fibro-cellular areas with necrotic centres present in the trabeculæ of the spleen in Banti's disease. Since then he has carried out further investigations on spleens from the various forms of splenomegalic disease. The book deals mainly with the author's own work on the subject, but the views and work of French observers are given full prominence, especially those of Professor Nanta who recently claimed to have demonstrated the mycelium of an aspergillus in the Gandy-Gamna nodules in Banti's disease. Following a chapter dealing generally with the splenomegalies there are chapters giving details of the cases investigated, the anatomical and histological appearances of the spleens, the results of splenic culture and the animal tests carried out with the various strains of streptothrix isolated from some of the spleens. The final chapter deals with the mycotic hypothesis of the cause of the splenomegalies and the contribution of French workers. The author is to be congratulated on the very convincing evidence he has produced that splenic anæmia, acholuric jaundice, and Banti's disease have a common etiology and that the causal organism is a streptothrix which invades the spleen. Apart from the other features the book is a veritable storehouse of general information on the splenomegalies, and the physician who has such cases under his care will find in it much that will be of interest and use to him. The illustrations are excellent and there is a good index and a long list of references.

**Nursing and Diseases of Sick Children.** By ALAN MONCRIEFF M.D., B.S., M.R.C.P. Pp. xvi., 550. Illustrated. London: H. K. Lewis & Co. Ltd. 1930. Price 15s.—This book is a product of the great Ormond Street school, and has been written by various members of the staff in collaboration with the Sister Tutor under the editorship of Dr. Moncrieff. Whether such an exhaustive knowledge of the diseases of sick children is necessary to a children's nurse is not for the reviewer to say. But, judging from the questions taken from the State Examinations and included in the book as an appendix, the examiners do not expect such details as the

book presents. It is difficult to see why nurses should be worried with such things as the various types of myopathies, the relationship between vaccinia and small-pox, or the pathogenesis and investigation of hydrocephalus. The sections on nursing are excellent. The book is very good as a reference book for children's nurses, but one cannot help feeling that as a text-book it is much too elaborate.

**Chronic Nasal Sinusitis and its Relation to General Medicine.** By P. WATSON-WILLIAMS, M.D. Pp. xvi., 221. 109 illustrations. Bristol: J. Wright & Sons Ltd. 1930. Price 15s.—Dr. Patrick Watson-Williams has enlarged his Semon Memorial Lecture, delivered in 1925, into an admirable book. The subject is one to which his long experience as a general physician before he became an oto-rhino-laryngologist has enabled him to do full justice. His object has been to point out the many toxæmias and secondary infections which may be the outcome of chronic nasal sinusitis. In this he has achieved a very real success because, in addition to a thorough understanding of nasal infections, whether manifest or latent, he is able from his wide knowledge to describe with clarity and precision the symptomatology of the resultant toxæmias and infections, more especially the mental disturbances associated with them. The clinical records which are included in this book furnish brief and striking illustrations of the manifold remote effects of focal sepsis in general and of nasal sepsis in particular. No psychiatrist, no physician and no general practitioner can afford to ignore the information contained in this book. Desultory references may be found in general literature to the systemic infections which depend upon chronic nasal sinusitis, but this is the first book devoted solely to the subject. The technique of nasal endoscopy, of diagnostic exploral suction of the sinuses and the remedial operations are well described and explained. The illustrations are numerous and good. Dr. Watson-Williams deserves hearty congratulations on having written a pioneer work.

**Essays and Addresses: Sociological, Biological and Psychological.** By A SURGEON. Pp. xiii., 277. London: H. K. Lewis & Co. Ltd. 1930. Price 10s. 6d.—These essays vary considerably in interest and importance, but several underlying principles can be traced throughout the series. The importance of the part played by evolution in the most fundamental of human affairs, both in the mental and physical

spheres of individual social life, is the keynote. It is forcibly emphasized that all attempts to promote human progress must be based on hereditary constitution and innate capacity. The pressing need of a wider diffusion of biological knowledge in the framing of social legislation and national life is one of their chief notes, and a plea is put forward for a census of the quality as well as the quantity of the nation. An interesting theory is advanced to explain the origin of " use acquirements " through variation and selection occurring among the intra-cellular units of which the animal cell is composed. There is much of value and interest to be found therein, and those interested in these subjects will be well repaid by their perusal.

# Editorial Notes

**British Association Meeting**

For the fourth time in its history the British Association for the Advancement of Science has met in Bristol.

The previous occasions were in 1836, 1875 and 1898. On the last occasion Dr. Bertram Rogers acted as one of the local Secretaries, and he achieved the distinction (together with the burden) of occupying the same office in 1930. The success of the meeting must have been most gratifying to all the officers of the Association both of the General Council and the Local Committees. The membership reached the high figure of 2,650, and the satisfaction expressed with all the arrangements was universal. The University buildings provided wonderful accommodation for the comfort of members and for the meetings of the various sections. Professor F. O. Bower, F.R.S., opened the Session with an inaugural address on "Size and Form in Plants" to a crowded and appreciative audience in the Colston Hall on Wednesday, 3rd September, whilst the final ceremony of the meeting was a special congregation of the University to confer upon him, as President of the Association, the honorary degree of D.Sc. Apart from the papers read at the various sections, there were many public lectures of the highest importance. The most interesting to members of the Medico-Chirurgical Society was undoubtedly that delivered by Sir Arthur Keith on "John Beddoe." This great anthropologist, to whose labours Sir Arthur Keith paid just tribute, was one of the first members of this Society and a man whose pre-eminence was amply

recognized in Bristol during his lifetime. Sir Arthur made the suggestion that a Chair of Anthropology should be founded in memory of Beddoe. It is hoped that the University will carry the suggestion into effect. Anthropology is far more than a mere delving into antiquity, it is one of the most living of the "humanities," and promises to furnish information of the utmost value to Sociology.

The numerous excursions into the country surrounding Bristol aroused the most enthusiastic praise from the members of the Association. The surprise expressed by some recalled an entry in the Diary of Joseph Farington (dated 1808, February 28th): "Fuseli was last week at Clifton near Bristol and raved about the romantic scenery, saying 'It was the finest thing in the kingdom, sublime, etc.' West repeated what he had often said before, 'That the country included within twenty miles of Bath contained more variety of landscape and noble scenes than any other county that could be mentioned.'" Judging from the comments of our visitors, the verdicts of Fuseli and Benjamin West still hold good.

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**The late Rev. H. N. Burden, Warden of the National Institutions for Persons requiring Care and Control.**

INSPIRED partly, no doubt, by the very nature of his profession, but infinitely more by a personal sense of humanitarianism, the late Reverend H. N. Burden early in life embarked upon a career of practical philanthropy. Accident of opportunity, combined with friendships with those similarly interested, first directed Mr. Burden's attention to the pitiful lot of the confirmed inebriate. To think was to act, and accordingly a

small Home for Inebriates was opened at Horfield, Bristol, within the shadow of the prison gates, and this was soon followed by the acquisition, through his efforts and for the same purpose, of what is now the Brentry Colony for Mental Defectives.

From this small beginning have sprung the magnificent—and the adjective is not ill-chosen—Homes for the Mentally Defective now to be found within and around the City of Bristol. Mr. Burden found, as others have since done, that inebriety is more frequently the result of mental deficiency than its cause, and so the transition from one to the other was a natural and almost inevitable result of Mr. Burden's broad-minded philanthropy for the benefit of his less fortunately endowed fellow-beings.

From the time Mr. Burden first joined the Royal Commission on Mental Deficiency more than twenty years ago he unceasingly devoted his time, his money, and his undoubted business acumen to the betterment of the study, housing, and treatment of the mentally defective child and adolescent. Family mansions within the Bristol area and other parts of the country were, as they came into the market, gradually acquired by him for the benefit of the nation's unfortunates. The splendid properties of Stoke Park, Leigh Court, Stapleton Park (known as Beech House), Whittington Hall, and others of less note, were purchased privately by Mr. Burden without any assistance from rates, donations, or public or private grants of any sort, and devoted to his great objective, and all without ostentation, publicity, or proclamation from the housetops of the grandeur of the conception and the nobility of the charity. So quietly indeed did Mr. Burden achieve his good deeds that his intentions are not yet quite clearly recognized even in Bristol. But these

were at least two-fold; one, the foundation of a series of national institutions for national purposes, and the other, the prosecution of study and research into mental deficiency. His first main objective is already largely achieved, for the several properties have been vested in trustees under a trust deed with instructions for their use for any national philanthropic purpose.

The cause of the mentally defective Mr. Burden had ever at heart and his second objective, achieved almost on his death-bed, was the organization on a liberal scale of medical and scientific research into mental deficiency, to be associated, with the consent of the authorities, with the University of Bristol. The names of the men to whom this task of research into a great and pressing national problem have already been announced, to which now falls to be added that of Dr. R. G. Gordon of Bath. To them there is now given a great opportunity, and no one, knowing to whom this task has been entrusted, can doubt that their ultimate researches into the origins, causes, concomitants, and possible remedial measures of mental deficiency will do credit to the memory of the late Warden of Stoke Park Colony, and will worthily uphold the traditions and prestige of the City and University of Bristol.

As we go to press we learn that the Trustees have, with the approval of the Secretary of State, appointed Mrs. Rosa Gladys Burden, of Clevedon Hall, to be Warden of the National Institutions in succession to the late Rev. Harold Nelson Burden.

R. J. A. B.

# The Medical Library of the University of Bristol,

WITH WHICH IS INCORPORATED

**The Library of the Bristol Medico-Chirurgical Society.**

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*The following donations have been received since the publication of the list in June, 1930.*

October, 1930.

| | |
|---|---|
| American Laryngological, Rhinological and Otological Society (1) .. .. .. | 1 volume |
| American Otological Society (2) .. .. | 1 ,, |
| Association des Médecins de Langue Française (3) .. .. .. .. .. .. | 1 ,, |
| Dr. W. S. Bainbridge (4) .. .. .. | 1 ,, |
| British Medical Association (5) .. .. | 1 pamphlet |
| Director-General, Army Medical Services (6) | 1 volume |
| Professor E. W. Hey Groves (7) .. .. | 11 volumes |
| Japanese Embassy (8) .. .. .. .. | 2 ,, |
| Munro Smith Memorial Fund (9) .. .. | 1 volume |
| Philadelphia Committee for Clinical Study of Opium Addiction (10) .. .. .. | 1 ,, |
| Rockefeller Foundation (11) .. .. .. | 1 ,, |
| Surgeon-General of U.S. Army (12) .. .. | 1 ,, |
| University of Glasgow (13) .. .. .. | 1 ,, |
| University of Otago (14) .. .. .. | 1 ,, |

Unbound periodicals have also been received from Professor Hey Groves.

## THE ONE HUNDRED AND THIRTY-THIRD LIST OF BOOKS.

The figures in round brackets refer to the figures after the names of the donors. The books to which no such figures are attached have either been bought from the Library Fund or received through the *Journal*.

| | | | |
|---|---|---|---|
| **Adachi, B.** .. .. .. | *Das Arteriensystem der Japaner.* 2 Vols. | (8) | 1928 |
| **Ballance, C.** .. .. .. | *Dawn and Epic of Neurology and Surgery* | (13) | 1930 |
| **Bland-Sutton, Sir J.** .. | *Story of a Surgeon* .. .. .. .. .. | (7) | 1930 |
| **Beeston, G. N.** .. .. | *Conjoint Finals* .. .. .. .. .. .. .. | | 1930 |
| **Bourne, A.** .. .. .. | *Recent Advances in Obstetrics and Gynæcology* | (9) | 1928 |
| *B.M.A. Proposals for a General Medical Service for the Nation* .. | | (5) | 1930 |
| **Brockbank, E. M.**.. .. | *Diagnosis and Treatment of Heart Disease* 6th Ed. | | 1930 |

**Bruns, O., and Thiel, K.** *Die Wiederbelebung* .. .. .. .. .. (7) 1930
**Gibson, A. G.** .. .. *Mycoses of the Spleen* .. .. .. .. .. .. 1930
**Gordon-Taylor, G.** .. *The Dramatic in Surgery* .. .. .. .. .. 1930
**Gordon, R. G., and Thomson, F. G.** *Physiological Principles of Hydrology* 1930
**Haumann, W.** .. .. *Die Wirbelbruche und ihre Endergebnisse* .. (7) 1930
**Hermannsdorfer, A.** .. *Die Diätetische Vor-und Nachkur bei der Operativen Behandlung der Lungentuberkulose* (7) 1929
**Groves, E. W. H.** .. *Synopsis of Surgery* .. .. .. .. 9th Ed. 1930
**Kromayer, E.** .. .. *Cosmetic Treatment of Skin Complaints* .. .. 1930
**Larkin, A. J.** .. .. *Radium in General Practice* .. .. .. .. 1929
**Leriche, A., and Policard, A.** *Physiologie, Pathologique Chirurgicale* (7) 1930
**Lloyd-Williams, A.** .. *The Doctor's Job* .. .. .. .. .. .. .. 1930
**Love, R. J. M.** .. .. *A Shorter Surgery* .. .. .. 2nd Ed. 1930
**McCann, F. J.** .. .. *Contraception a Common Cause of Disease* .. 1928
**Mackenzie, Sir C.** .. *Action of Muscles* .. .. .. .. 2nd Ed. 1930
**Martindale and Westcott** *Extra Pharmacopœia* Vol. 2. .. 19th Ed. 1929
*Modern Technique in Treatment.* Vols. 1 and 2 .. .. .. .. .. 1928
**Moncrieff, A.** (ed.) .. *Nursing and Diseases of Children* .. .. .. 1930
**Nauth, B.** .. .. .. *All-India Medical Conference* .. .. .. (7) 1929
*Opium Addiction* .. .. .. .. .. .. .. .. .. .. .. .. (10) 1929
**Pellegrini, A.** .. .. *Cinematizzioni* .. .. .. .. .. .. (7) 1929
*Pharmacopœia of the Central London Ophthalmic Hospital* .. .. .. .. 1930
**Ray, K. S.** .. .. .. *Some Problems of Medical Profession in India* (7) —
**Sauerbruch, F.** .. .. *Chirurgie der Brustorgane.* I.i. .. .. (7) 1930
**Scott, G. L.** .. .. .. *The Morphine Habit* .. .. .. .. .. .. 1930
**Sechehaye, A.** .. .. *The Treatment of Tuberculosis with Umckaloabo* —
**Smith, F.** .. .. .. *Short History of the R.A.M.C.* .. .. .. (6) 1929
**Stuart-Low, G.** .. .. *Nasal Catarrh* .. .. .. .. .. .. .. 1930

## TRANSACTIONS, REPORTS, JOURNALS, ETC.

Association des Médecins de Langue Française Congrés, 1929 .. .. —
Collected Papers of the Lockwood Clinic, 1929 .. .. .. .. .. (7) —
Collected Papers of the Mayo Clinic. Vol. 21 .. .. .. .. .. .. 1929
Index Catalogue Surgeon-General's Library. 3rd Series, Vol. 8 .. (12) 1929
Medical Annual, 1930 .. .. .. .. .. .. .. .. .. .. .. .. —
Methods and Problems of Medical Education. 17th Series .. .. (11) 1930
Proceedings of the University of Otago Medical School. Vol. 7 .. (14) 1930
Progressive Medicine. June, 1930 .. .. .. .. .. .. .. .. .. .. —
Report of 5th International Congress of Military Medicine and Pharmacy, 1929 .. .. .. .. .. .. .. .. .. .. .. .. .. .. .. (4) —
St. Thomas's Hospital Reports. Vol. 52 .. .. .. .. .. .. .. 1930
*Société Internationale de Chirurgie.* VIIIe Congres. Vol. 1 .. .. (7) 1929
Surgical Clinics of N. America. Vol. 10. Nos. 3 and 4 .. .. .. .. 1930
Transactions of the American Laryngological, Rhinological and Otological Society. Vol. 35 .. .. .. .. .. .. .. .. .. .. .. (1) 1929
Transactions of the American Otological Society. Vol. 19 .. .. (2) 1929
Transactions of the College of Physicians of Philadelphia. 3rd Series, Vol. 51 1929

# Local Medical Notes.

**Long Fox Memorial Lecture.**—The Vice-Chancellor, Thomas Loveday, LL.D., in the Chair. The Eighteenth Annual Lecture will be delivered on Tuesday, October 28th, 1930, at 5.15 p.m., in the Physiological Lecture Theatre of the University, by Professor J. A. Nixon, C.M.G., M.D., F.R.C.P. Subject: "The Influence of Food on the Production and Prevention of Disease." Tea will be served at 4.30 p.m. for those intimating to the Dean of the Medical Faculty their intention of being present.

EXAMINATION RESULTS.

**University of Bristol.**—Students of the University have recently passed the following examinations:—

M.B., Ch.B.—*First Examination. Pass:* F. C. Collingwood, Theodora M. Crabtree, A. E. Jowett, S. D. Loxton, M. A. Nicholson, B. Ridgway. *In Physics (Completing Examination):* J. R. G. Damrel, Irene G. Hamilton, T. H. Taylor, Ursula W. Wood. *In Biology (Completing Examination):* A. C. Molden. *In Botany (Completing Examination):* A. J. Matheson.

B.D.S.—*First Examination. Pass:* Kathleen G. Brimelow.

L.D.S.—*Preliminary Science Examination. Pass: In Biology (Completing Examination):* J. G. Clancy, R. J. Lee.

Conjoint Board.—L.D.S., R.C.S.—*Final Examination. Part I. Pass:* I. M. Ayliffe, D. R. Jones. *Part II. Pass:* W. Forsyth, W. F. G. Harvey, W. R. R. Mewton, K. V. M. Taylor-Milton.